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(54) Title: HYDROXYLAMINE SUBSTITUTED IMIDAZO RING COMPOUNDS

(57) Abstract: Imidazo ring compounds (e.g., imidazoquinolines, 6, 7, 8, 9-tetrahydroimidazoquinolines, imidazonaphthyridines, and imidazopyridines) with a hydroxylamine substituent at the 2-position, pharmaceutical compositions containing the compounds, intermediates, and methods of use of these compounds as immunomodulators, for inducing cytokine biosynthesis in animals and in the treatment of diseases including viral and neoplastic diseases are disclosed.

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HYDROXYLAMINE SUBSTITUTED IMIDAZO RING COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application claims priority to U.S. Provisional Application Serial No. 60/520,215, filed on November 14, 2003, which is incorporated herein in its entirety.

BACKGROUND

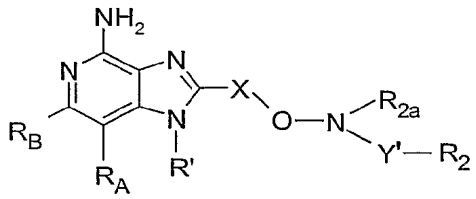
In the 1950's the 1*H*-imidazo[4,5-*c*]quinoline ring system was developed, and 1-(6-methoxy-8-quinolinyl)-2-methyl-1*H*-imidazo[4,5-*c*]quinoline was synthesized for possible use as an antimalarial agent. Subsequently, syntheses of various substituted 1*H*-imidazo[4,5-*c*]quinolines were reported. For example, 1-[2-(4-piperidyl)ethyl]-1*H*-imidazo[4,5-*c*]quinoline was synthesized as a possible anticonvulsant and cardiovascular agent. Also, several 2-oxoimidazo[4,5-*c*]quinolines have been reported.

Certain 1*H*-imidazo[4,5-*c*]quinolin-4-amines and 1- and 2-substituted derivatives thereof were later found to be useful as antiviral agents, bronchodilators and immunomodulators. Subsequently, certain substituted 1*H*-imidazo[4,5-*c*]pyridin-4-amine, quinolin-4-amine, tetrahydroquinolin-4-amine, naphthyridin-4-amine, and tetrahydronaphthyridin-4-amine compounds as well as certain analogous thiazolo and oxazolo compounds were synthesized and found to be useful as immune response modifiers (IRMs), rendering them useful in the treatment of a variety of disorders.

There continues to be interest in and a need for compounds that have the ability to modulate the immune response, by induction of cytokine biosynthesis or other mechanisms.

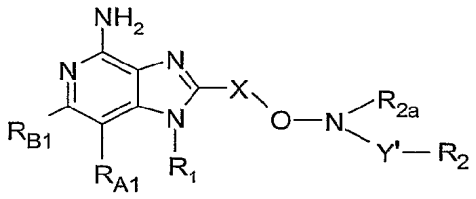
SUMMARY

The present invention provides a new class of compounds that are useful in inducing cytokine biosynthesis in animals. Such compounds are of the following Formula I:



I

and, more particularly, compounds of the following Formula II:



II

wherein: R', R_A, R_B, R_{A1}, R_{B1}, R_1, R_2, R_{2a}, X, and Y' are as defined below.

The compounds of Formulas I and II are useful as immune response modifiers (IRMs) due to their ability to induce cytokine biosynthesis (e.g., induce the biosynthesis or production of one or more cytokines) and otherwise modulate the immune response when administered to animals. This makes the compounds useful in the treatment of a variety of conditions, such as viral diseases and neoplastic diseases, that are responsive to such changes in the immune response.

In another aspect, the present invention provides pharmaceutical compositions containing the immune response modifier compounds, and methods of inducing cytokine biosynthesis in an animal, treating a viral disease in an animal, and treating a neoplastic disease in an animal, by administering an effective amount of one or more compounds of Formula I and/or Formula II and/or pharmaceutically acceptable salts thereof to the animal.

In another aspect, the invention provides methods of synthesizing compounds of Formulas I and II and intermediates useful in the synthesis of these compounds.

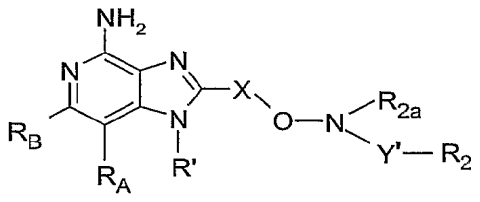
As used herein, "a," "an," "the," "at least one," and "one or more" are used interchangeably.

The terms "comprising" and variations thereof do not have a limiting meaning where these terms appear in the description and claims.

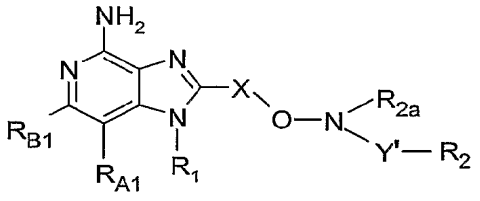
The above summary of the present invention is not intended to describe each disclosed embodiment or every implementation of the present invention. The description that follows more particularly exemplifies illustrative embodiments. Guidance is also provided herein through lists of examples, which can be used in various combinations. In each instance, the recited list serves only as a representative group and should not be interpreted as an exclusive list.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS OF THE INVENTION

The present invention provides compounds of the following Formulas I through VI:



I



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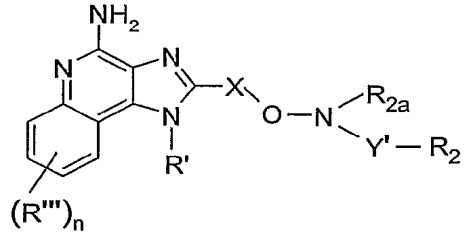
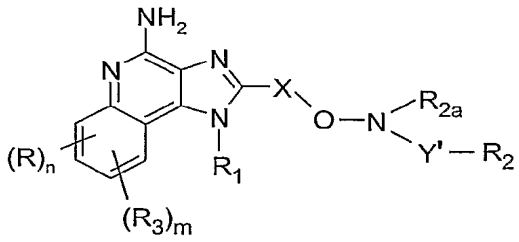
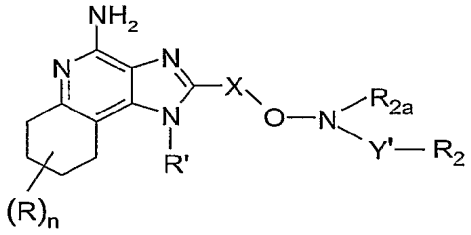


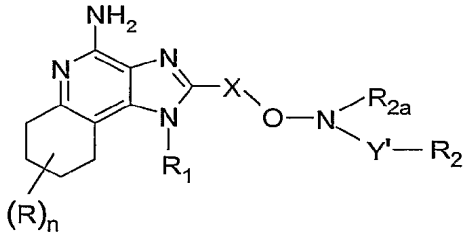
III



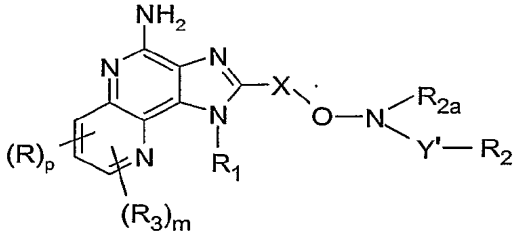
IIIa



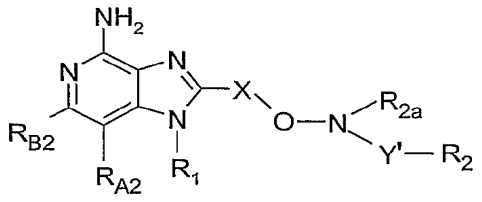
IV



IVa



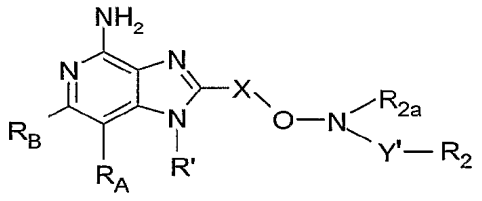
V



VI

wherein: R, R', R''', R_A, R_B, R_{A1}, R_{B1}, R_{A2}, R_{B2}, R_1, R_2, R_{2a}, R_3, n, m, p, X, and Y' are as defined below.

In one aspect of the invention, compounds are provided that are of the following Formula I:



I

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

R_A and R_B are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R''' groups;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated

ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

Y' is selected from the group consisting of:

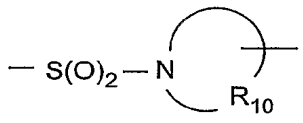
a bond,

-C(O)-,

-C(S)-,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,



,

-C(O)-O-,

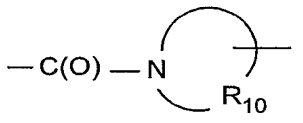
$-C(O)-N(R_8)-$,

$-C(S)-N(R_8)-$,

$-C(O)-N(R_8)-S(O)_2-$,

$-C(O)-N(R_8)-C(O)-$,

$-C(S)-N(R_8)-C(O)-$,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

$-C(=NH)-N(R_8)-$;

R_2 and R_{2a} are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

$-S(O)_{0-2}$-alkyl,

$-S(O)_{0-2}$-aryl,

$-NH-S(O)_2$-alkyl,

$-NH-S(O)_2$-aryl,

haloalkoxy,

halogen,

cyano,

nitro,

aryl,

heteroaryl,

heterocyclyl,

aryloxy,

arylalkyleneoxy,

-C(O)-O-alkyl,

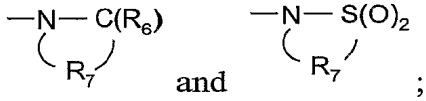
-C(O)-N(R_8)$_2$,

-N(R_8)-C(O)-alkyl,

-O-(CO)-alkyl, and

-C(O)-alkyl;

or R_2 and R_{2a} together with the nitrogen atom and Y' to which they are bonded can join to form a ring selected from the group consisting of:



and

;

R' is hydrogen or a non-interfering substituent;

R''' is a non-interfering substituent;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

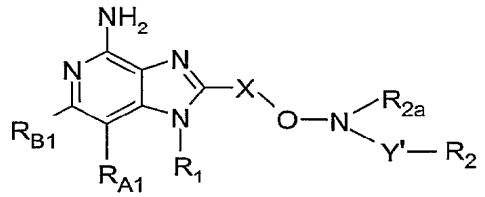
R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl; and

R_{10} is C_{3-8} alkylene;

or a pharmaceutically acceptable salt thereof.

In one aspect of the invention, compounds are provided that are of the following Formula II:



II

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

R_{A1} and R_{B1} are each independently selected from the group consisting of:

hydrogen,

halogen,
alkyl,
alkenyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

or when taken together, R_{A1} and R_{B1} form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group;

or when taken together, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,
hydroxy,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
$-N(R_9)_2$;

R_3 is selected from the group consisting of:

$-Z-R_4$,
$-Z-X'-R_4$,
$-Z-X'-Y-R_4$,
$-Z-X'-Y-X'-Y-R_4$, and
$-Z-X'-R_5$;

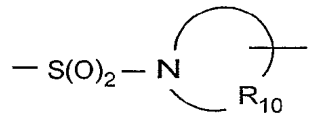
Y' is selected from the group consisting of:

a bond,
-C(O)-,

-C(S)-,

-$S(O)_2$-,

-$S(O)_2$-$N(R_8)$-,



,

-C(O)-O-,

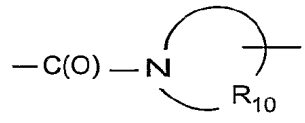
-C(O)-$N(R_8)$-,

-C(S)-$N(R_8)$-,

-C(O)-$N(R_8)$-$S(O)_2$-,

-C(O)-$N(R_8)$-C(O)-,

-C(S)-$N(R_8)$-C(O)-,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

-C(=NH)-$N(R_8)$-;

R_1 is selected from the group consisting of:

-R_4,

-X'-R_4,

-X'-Y-R_4,

-X'-Y-X'-Y-R_4,

-X'-R_5,

-X"-O-NR_{1a}-Y'-R_{1b}, and

-X"-O-N=C(R_1')(R_1");

R_{1a}, R_{1b}, R_1', R_1", R_2, and R_{2a} are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

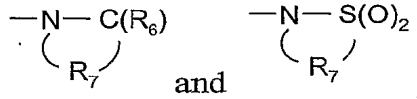
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
$-S(O)_{0-2}$-alkyl,
$-S(O)_{0-2}$-aryl,
$-NH-S(O)_2$-alkyl,
$-NH-S(O)_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
$-C(O)-N(R_8)_2$,
$-N(R_8)$-C(O)-alkyl,
-O-(CO)-alkyl, and

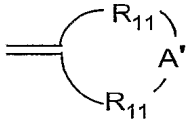
-C(O)-alkyl;

or R_{1a} and R_{1b} and/or R_2 and R_{2a} together with the nitrogen atom and Y' to which they are bonded can join to form a ring selected from the group consisting of:

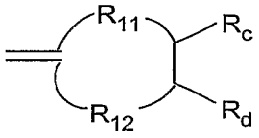


;

or R_1' and R_1" can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X" is $-CH(R_{13})$-alkylene- or $-CH(R_{13})$-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}$-,

$-S(O)_2-N(R_8)$-,

$-C(R_6)$-,

$-C(R_6)-O$-,

$-O-C(R_6)$-,

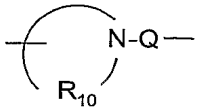
-O-C(O)-O-,

$-N(R_8)-Q$-,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,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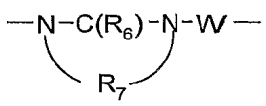
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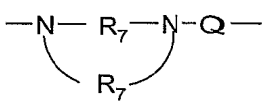
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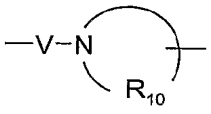
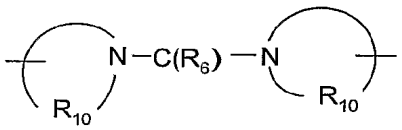
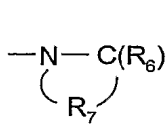

, and


;

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of: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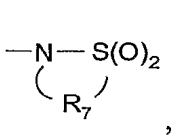
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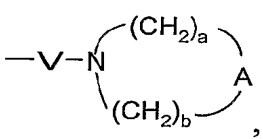
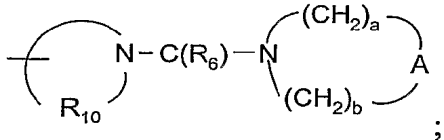

, and

;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

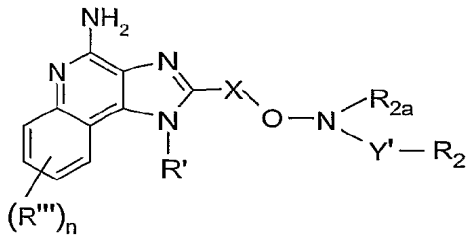
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$;

or a pharmaceutically acceptable salt thereof.

In one aspect of the invention, compounds are provided that are of the following Formula III:



III

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

Y' is selected from the group consisting of:

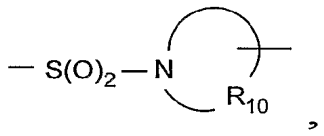
a bond,

-C(O)-,

-C(S)-,

-$S(O)_2$-,

-$S(O)_2$-$N(R_8)$-,



-C(O)-O-,

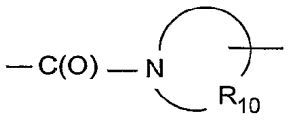
-C(O)-$N(R_8)$-,

-C(S)-$N(R_8)$-,

-C(O)-$N(R_8)$-$S(O)_2$-,

-C(O)-$N(R_8)$-C(O)-,

-C(S)-$N(R_8)$-C(O)-,



-C(O)-C(O)-,

-C(O)-C(O)-O-, and

-C(=NH)-$N(R_8)$-;

R_2 and R_{2a} are independently selected from the group consisting of:

hydrogen,
alkyl,
alkenyl,
aryl,
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:
hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
$-S(O)_{0-2}$-alkyl,
$-S(O)_{0-2}$-aryl,
$-NH-S(O)_2$-alkyl,
$-NH-S(O)_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,

-C(O)-O-alkyl,

-C(O)-N(R_8)$_2$,

-N(R_8)-C(O)-alkyl,

-O-(CO)-alkyl, and

-C(O)-alkyl;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_{10} is C_{3-8} alkylene;

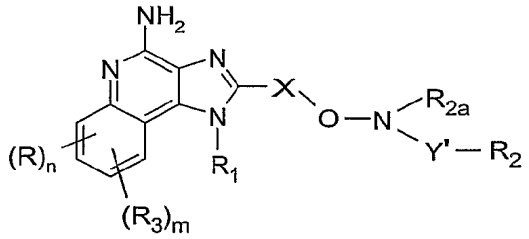
n is an integer from 0 to 4;

R''' is a non-interfering substituent; and

R' is hydrogen or a non-interfering substituent;

or a pharmaceutically acceptable salt thereof.

In one aspect of the invention, compounds are provided that are of the following Formula IIIa:



IIIa

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

Y' is selected from the group consisting of:

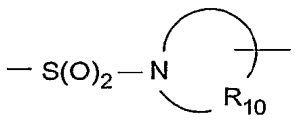
a bond,

-C(O)-,

-C(S)-,

-S(O)$_2$-,

-S(O)$_2$-N(R_8)-,



,

-C(O)-O-,

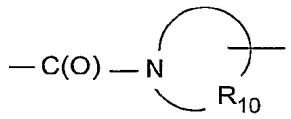
-C(O)-N(R_8)-,

-C(S)-N(R_8)-,

-C(O)-N(R_8)-S(O)$_2$-,

-C(O)-N(R_8)-C(O)-,

-C(S)-N(R_8)-C(O)-,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

-C(=NH)-N(R_8)-;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

R_1 is selected from the group consisting of:

-R_4,

-X'-R_4,

-X'-Y-R_4,

-X'-Y-X'-Y-R_4,

-X'-R_5,

-X"-O-NR_{1a}-Y'-R_{1b}, and

-X"-O-N=C(R_1')(R_1");

R_{1a}, R_{1b}, R_1', R_1", R_2, and R_{2a} are independently selected from the group consisting of:

hydrogen,

alkyl,
alkenyl,
aryl,
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:
hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
$-S(O)_{0-2}$-alkyl,
$-S(O)_{0-2}$-aryl,
$-NH-S(O)_2$-alkyl,
$-NH-S(O)_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,

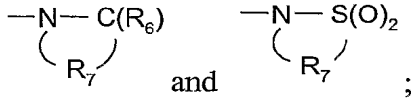
-C(O)-N(R_8)$_2$,

-N(R_8)-C(O)-alkyl,

-O-(CO)-alkyl, and

-C(O)-alkyl;

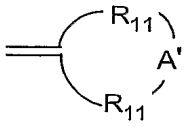
or R_{1a} and R_{1b} and/or R_2 and R_{2a} together with the nitrogen atom and Y' to which they are bonded can join to form a ring selected from the group consisting of:



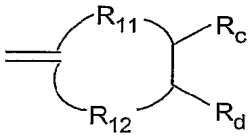
and

;

or R_1' and R_1" can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and –N(R_9)$_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

R_3 is selected from the group consisting of:

-Z-R_4,

-Z-X'-R_4,

-Z-X'-Y-R_4,

-Z-X'-Y-X'-Y-R_4, and

-Z-X'-R_5;

n is an integer from 0 to 4;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and

alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X" is $-CH(R_{13})$-alkylene- or $-CH(R_{13})$-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}$-,

$-S(O)_2-N(R_8)$-,

$-C(R_6)$-,

$-C(R_6)-O$-,

$-O-C(R_6)$-,

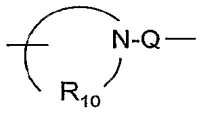
-O-C(O)-O-,

$-N(R_8)-Q$-,

$-C(R_6)-N(R_8)$-,

$-O-C(R_6)-N(R_8)$-,

$-C(R_6)-N(OR_9)$-,



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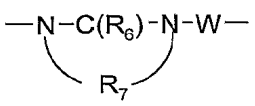

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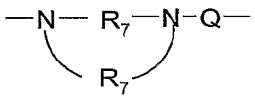

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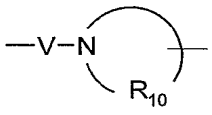
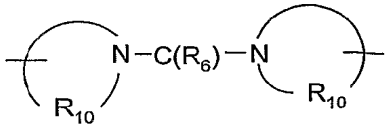


, and



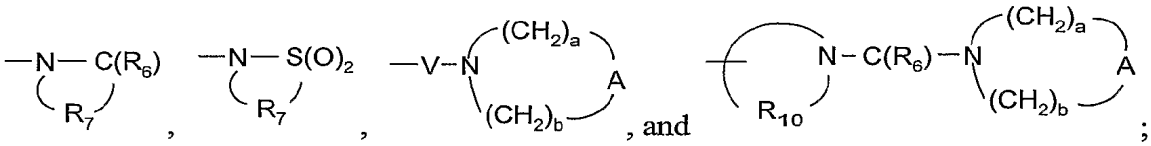
;

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl,

alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and

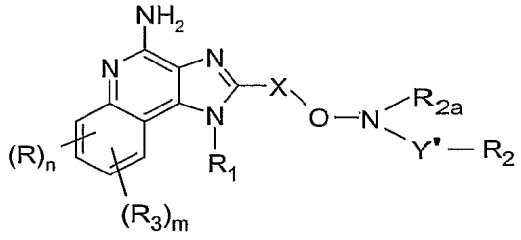
$-S(O)_2-$;

W is selected from the group consisting of a bond, $-C(O)-$, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In one aspect of the invention, compounds are provided that are of the following Formula IIIa:



IIIa

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

Y' is selected from the group consisting of:

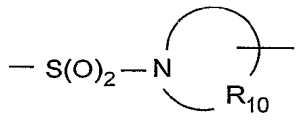
a bond,

$-C(O)-$,

$-C(S)-$,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,



,

$-C(O)-O-$,

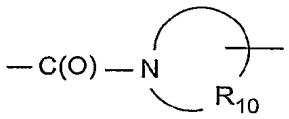
$-C(O)-N(R_8)-$,

$-C(S)-N(R_8)-$,

$-C(O)-N(R_8)-S(O)_2-$,

$-C(O)-N(R_8)-C(O)-$,

$-C(S)-N(R_8)-C(O)-$,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

-C(=NH)-N(R_8)-;

R_2 and R_{2a} are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

-$S(O)_{0-2}$-alkyl,

-$S(O)_{0-2}$-aryl,

-NH-$S(O)_2$-alkyl,

-NH-$S(O)_2$-aryl,

haloalkoxy,

halogen,

cyano,

nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R_8)$_2$,
-N(R_8)-C(O)-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

R is selected from the group consisting of:

halogen,
hydroxy,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
-N(R_9)$_2$;

R_1 is selected from the group consisting of:

-R_4,
-X'-R_4,
-X'-Y-R_4,
-X'-Y-X'-Y-R_4,
-X'-R_5,
-X"-O-NH-Y'-R_1', and
-X"-O-N=C(R_1')(R_1");

R_3 is selected from the group consisting of:

-Z-R_4,
-Z-X'-R_4,

-Z-X'-Y-R_4,

-Z-X'-Y-X'-Y-R_4, and

-Z-X'-R_5;

n is an integer from 0 to 4;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X" is –CH(R_{13})-alkylene- or –CH(R_{13})-alkenylene-;

Y is selected from the group consisting of:

-$S(O)_{0-2}$-,

-$S(O)_2$-N(R_8)-,

-C(R_6)-,

-C(R_6)-O-,

-O-C(R_6)-,

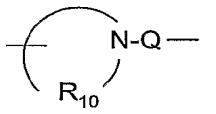
-O-C(O)-O-,

-N(R_8)-Q-,

-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

-C(R_6)-N(OR_9)-,



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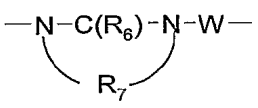

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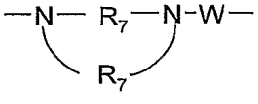

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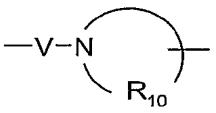
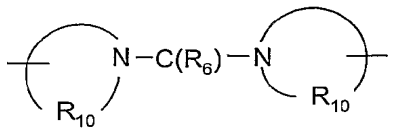


, and

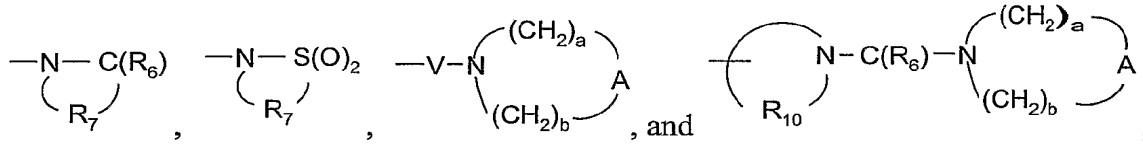


;

Z is a bond or -O-;

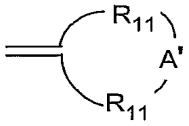
R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:

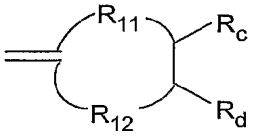


;

R_1' and R_1'' are independently the same as R_2, or R_1' and R_1'' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

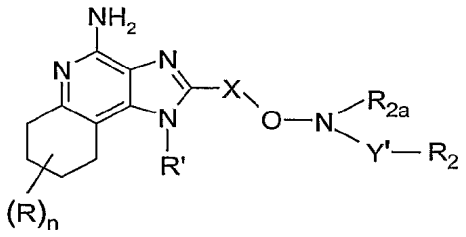
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$;

or a pharmaceutically acceptable salt thereof.

In one aspect of the invention, compounds are provided that are of the following Formula IV:



IV

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

Y' is selected from the group consisting of:

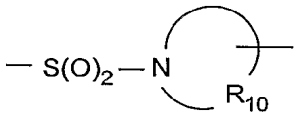
a bond,

-C(O)-,

-C(S)-,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,



,

-C(O)-O-,

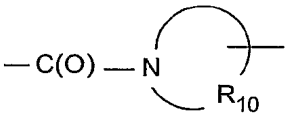
$-C(O)-N(R_8)-$,

$-C(S)-N(R_8)-$,

$-C(O)-N(R_8)-S(O)_2-$,

$-C(O)-N(R_8)-C(O)-$,

$-C(S)-N(R_8)-C(O)-$,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

$-C(=NH)-N(R_8)-$;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

n is an integer from 0 to 4;

R_2 and R_{2a} are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

$-S(O)_{0-2}$-alkyl,

$-S(O)_{0-2}$-aryl,

$-NH-S(O)_2$-alkyl,

$-NH-S(O)_2$-aryl,

haloalkoxy,

halogen,

cyano,

nitro,

aryl,

heteroaryl,

heterocyclyl,

aryloxy,

arylalkyleneoxy;

-C(O)-O-alkyl,

-C(O)-N(R_8)$_2$,

-N(R_8)-C(O)-alkyl,

-O-(CO)-alkyl, and

-C(O)-alkyl;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

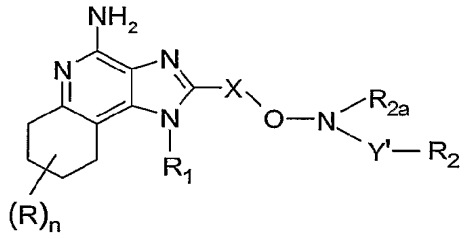
R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene; and

R' is hydrogen or a non-interfering substituent;

or a pharmaceutically acceptable salt thereof.

In one aspect of the invention, compounds are provided that are of the following Formula (IVa):



IVa

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

Y' is selected from the group consisting of:

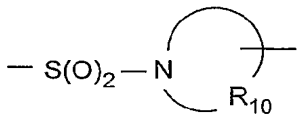
a bond,

-C(O)-,

-C(S)-,

-S(O)$_2$-,

-S(O)$_2$-N(R_8)-,



,

-C(O)-O-,

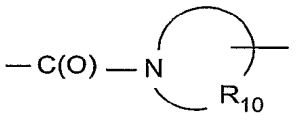
-C(O)-N(R_8)-,

-C(S)-N(R_8)-,

-C(O)-N(R_8)-$S(O)_2$-,

-C(O)-N(R_8)-C(O)-,

-C(S)-N(R_8)-C(O)-,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

-C(=NH)-N(R_8)-;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

R_1 is selected from the group consisting of:

-R_4,

-X'-R_4,

-X'-Y-R_4,

-X'-Y-X'-Y-R_4,

-X'-R_5,

-X"-O-NR_{1a}-Y'-R_{1b}, and

-X"-O-N=C(R_1')(R_1");

R_{1a}, R_{1b}, R_1', R_1'', R_2, and R_{2a} are independently selected from the group consisting of:

hydrogen,
alkyl,
alkenyl,
aryl,
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
-$S(O)_{0-2}$-alkyl,
-$S(O)_{0-2}$-aryl,
-NH-$S(O)_2$-alkyl,
-NH-$S(O)_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,

aryloxy,

arylalkyleneoxy,

-C(O)-O-alkyl,

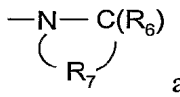
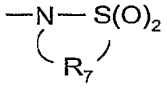
-C(O)-N(R_8)$_2$,

-N(R_8)-C(O)-alkyl,

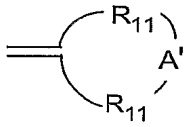
-O-(CO)-alkyl, and

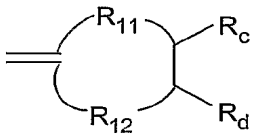
-C(O)-alkyl;

or R_{1a} and R_{1b} and/or R_2 and R_{2a} together with the nitrogen atom and Y' to which they are bonded can join to form a ring selected from the group consisting of:


and

;

or R_1' and R_1" can join together to form a ring system selected from the group consisting of:


wherein the total number of atoms in the ring is 4 to 9, and


wherein the total number of atoms in the ring is 4 to 9;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and –N(R_9)$_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

n is an integer from 0 to 4;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X" is –CH(R_{13})-alkylene- or –CH(R_{13})-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

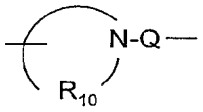
-O-C(O)-O-,

-$N(R_8)$-Q-,

-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

-$C(R_6)$-$N(OR_9)$-,



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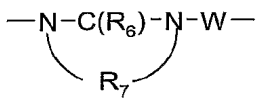

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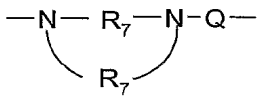

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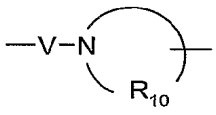

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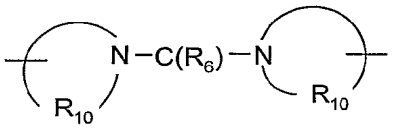
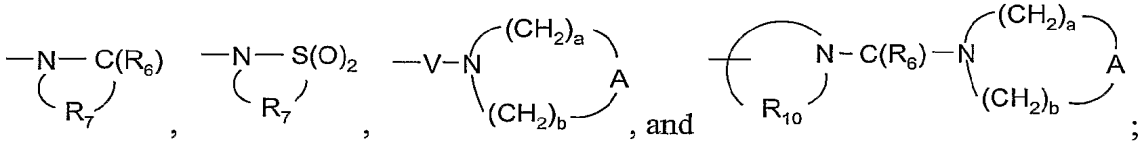


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino,

(dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-CH_2$-, -O-, -C(O)-, -$S(O)_{0-2}$-, and $-N(R_4)$-;

A' is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -N(-Q-R_4)-, and -CH_2-;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, and -$C(R_6)$-$N(OR_9)$-;

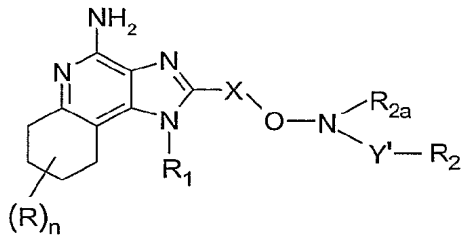
V is selected from the group consisting of -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In one aspect of the invention, compounds are provided that are of the following Formula IVa:



IVa

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

Y' is selected from the group consisting of:

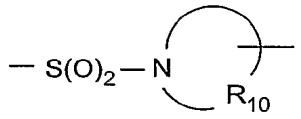
a bond,

-C(O)-,

-C(S)-,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,



,

-C(O)-O-,

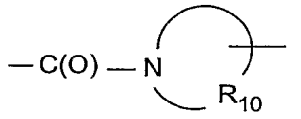
$-C(O)-N(R_8)-$,

$-C(S)-N(R_8)-$,

$-C(O)-N(R_8)-S(O)_2-$,

$-C(O)-N(R_8)-C(O)-$,

$-C(S)-N(R_8)-C(O)-$,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

-C(=NH)-$N(R_8)$-;

R_2 and R_{2a} are independently selected from the group consisting of:

hydrogen,
alkyl,
alkenyl,
aryl,
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:
hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
$-S(O)_{0-2}$-alkyl,
$-S(O)_{0-2}$-aryl,
$-NH-S(O)_2$-alkyl,
$-NH-S(O)_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy;

-C(O)-O-alkyl,

-C(O)-N(R_8)$_2$,

-N(R_8)-C(O)-alkyl,

-O-(CO)-alkyl, and

-C(O)-alkyl;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

n is an integer from 0 to 4;

R_1 is selected from the group consisting of:

-R_4,

-X'-R_4,

-X'-Y-R_4,

-X'-Y-X'-Y-R_4,

-X'-R_5,

-X"-O-NH-Y'-R_1', and

-X"-O-N=C(R_1')(R_1");

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X" is –CH(R_{13})-alkylene- or –CH(R_{13})-alkenylene-;

Y is selected from the group consisting of:

-S(O)$_{0-2}$-,

-S(O)$_2$-N(R_8)-,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

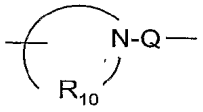
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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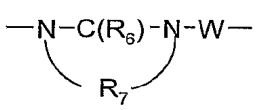

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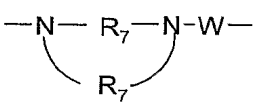

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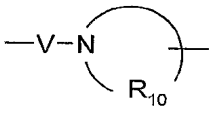
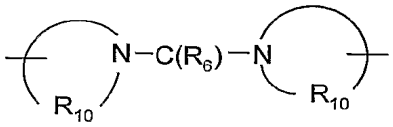


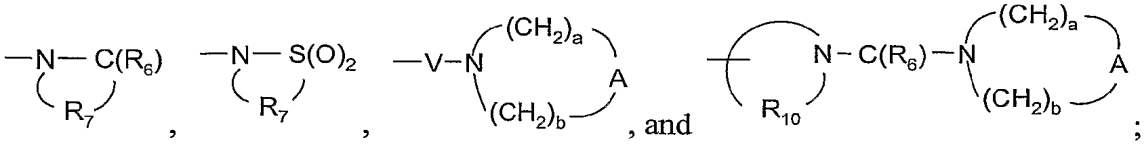
, and



;

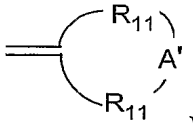
R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:

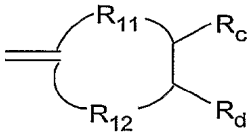


;

R_1' and R_1'' are independently R_2, or R_1' and R_1'' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -N(-Q-R_4)-, and -CH_2-;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, and -$C(R_6)$-$N(OR_9)$-;

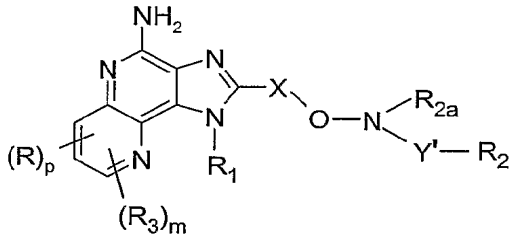
V is selected from the group consisting of -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and –$S(O)_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In one aspect of the invention, compounds are provided that are of the following Formula V:



V

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

Y' is selected from the group consisting of:

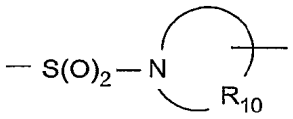
a bond,

-C(O)-,

-C(S)-,

-$S(O)_2$-,

-$S(O)_2$-$N(R_8)$-,



,

-C(O)-O-,

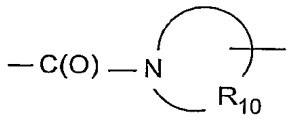
-C(O)-$N(R_8)$-,

-C(S)-$N(R_8)$-,

-C(O)-$N(R_8)$-$S(O)_2$-,

-C(O)-N(R_8)-C(O)-,

-C(S)-N(R_8)-C(O)-,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

-C(=NH)-N(R_8)-;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

R_1 is selected from the group consisting of:

-R_4,

-X'-R_4,

-X'-Y-R_4,

-X'-Y-X'-Y-R_4,

-X'-R_5,

-X"-O-NR_{1a}-Y'-R_{1b}, and

-X"-O-N=C(R_1')(R_1");

R_{1a}, R_{1b}, R_1', R_1", R_2, and R_{2a} are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

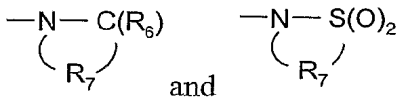
arylalkylenyl,

heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

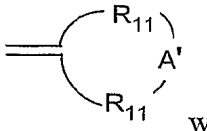
hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
$-S(O)_{0-2}$-alkyl,
$-S(O)_{0-2}$-aryl,
$-NH-S(O)_2$-alkyl,
$-NH-S(O)_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
$-C(O)-N(R_8)_2$,
$-N(R_8)-C(O)$-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

or R_{1a} and R_{1b} and/or R_2 and R_{2a} together with the nitrogen atom and Y' to which they are bonded can join to form a ring selected from the group consisting of:

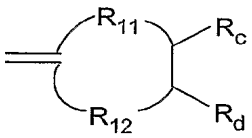


and ;

or R_1' and R_1" can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

R_3 is selected from the group consisting of:

-Z-R_4,

-Z-X'-R_4,

-Z-X'-Y-R_4,

-Z-X'-Y-X'-Y-R_4, and

-Z-X'-R_5;

p is an integer from 0 to 3;

m is 0 or 1, with the proviso that when m is 1, p is 0 or 1;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X" is $-CH(R_{13})$-alkylene- or $-CH(R_{13})$-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

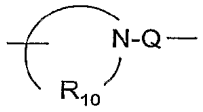
-O-C(O)-O-,

-$N(R_8)$-Q-,

-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

-$C(R_6)$-$N(OR_9)$-,



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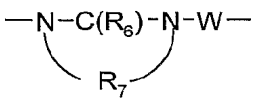

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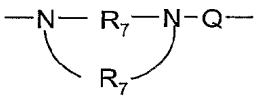

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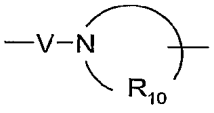
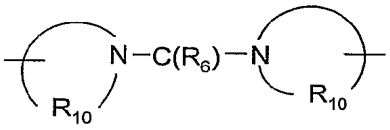


, and



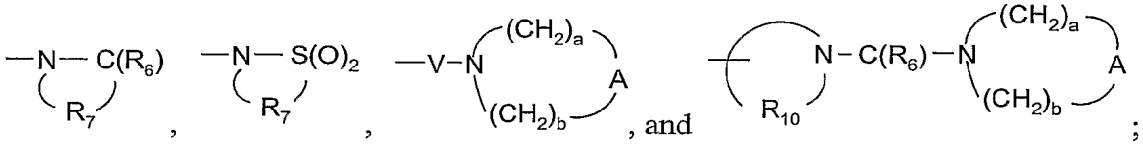
;

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy,

heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-CH_2$-, -O-, -C(O)-, -$S(O)_{0-2}$-, and $-N(R_4)$-;

A' is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -N(-Q-R_4)-, and -CH_2-;

Q is selected from the group consisting of a bond, -$C(R_6)$-, -$C(R_6)$-$C(R_6)$-, -$S(O)_2$-, -$C(R_6)$-$N(R_8)$-W-, -$S(O)_2$-$N(R_8)$-, -$C(R_6)$-O-, and -$C(R_6)$-$N(OR_9)$-;

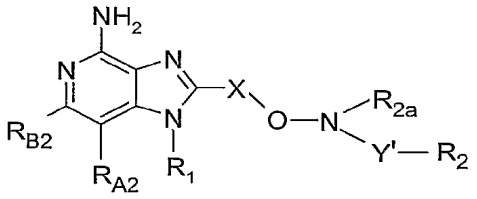
V is selected from the group consisting of -$C(R_6)$-, -O-$C(R_6)$-, -$N(R_8)$-$C(R_6)$-, and -$S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

In one aspect of the invention, compounds are provided that are of the following Formula VI:



VI

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

R_{A2} and R_{B2} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

Y' is selected from the group consisting of:

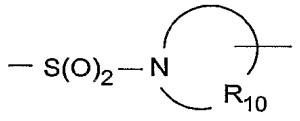
a bond,

-C(O)-,

-C(S)-,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,



,

-C(O)-O-,

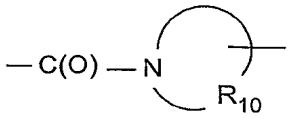
$-C(O)-N(R_8)-$,

$-C(S)-N(R_8)-$,

$-C(O)-N(R_8)-S(O)_2-$,

$-C(O)-N(R_8)-C(O)-$,

$-C(S)-N(R_8)-C(O)-$,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

-C(=NH)-N(R_8)-;

R_1 is selected from the group consisting of:

-R_4,

-X'-R_4,

-X'-Y-R_4,

-X'-Y-X'-Y-R_4,

-X'-R_5,

-X"-O-NR_{1a}-Y'-R_{1b}, and

-X"-O-N=C(R_1')(R_1");

R_{1a}, R_{1b}, R_1', R_1", R_2, and R_{2a} are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

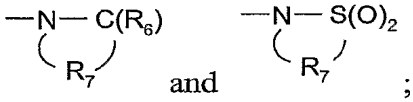
alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,
dialkylamino,
-S(O)$_{0-2}$-alkyl,
-S(O)$_{0-2}$-aryl,
-NH-S(O)$_2$-alkyl,
-NH-S(O)$_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R_8)$_2$,
-N(R_8)-C(O)-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

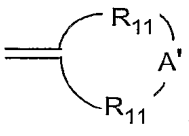
or R_{1a} and R_{1b} and/or R_2 and R_{2a} together with the nitrogen atom and Y' to which they are bonded can join to form a ring selected from the group consisting of:



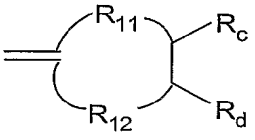
and

;

or R_1' and R_1" can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X" is $-CH(R_{13})$-alkylene- or $-CH(R_{13})$-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

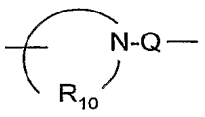
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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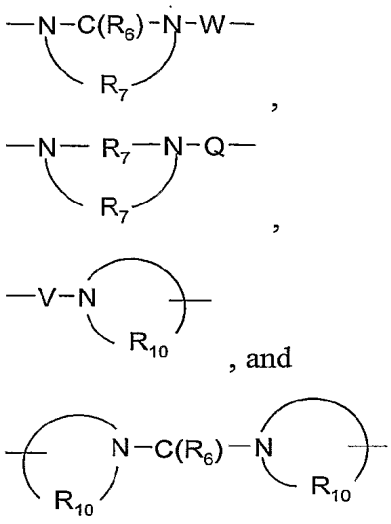
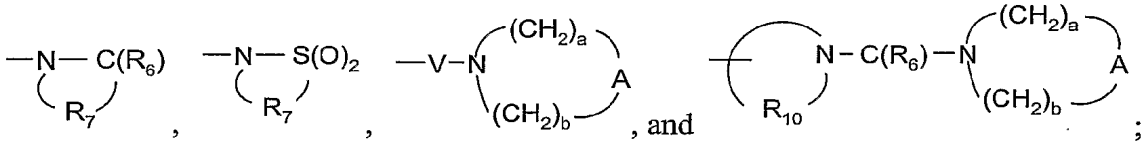


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$;

or a pharmaceutically acceptable salt thereof.

Certain embodiments of the present invention include non-interfering substituents. For example, in certain embodiments, R' is hydrogen or a non-interfering substitutent, and in certain embodiments, R''' is a non-interfering substituent.

Herein, "non-interfering" means that the ability of the compound or salt, which includes a non-interfering substituent, to modulate (e.g., induce or inhibit) the biosynthesis of one or more cytokines is not destroyed by the non-interfering substitutent. Illustrative non-interfering R' groups include those described herein for R_1. Illustrative non-interfering R''' groups include those described herein for R and R_3.

As used herein, the terms "alkyl", "alkenyl", "alkynyl" and the prefix "alk-" are inclusive of both straight chain and branched chain groups and of cyclic groups, i.e. cycloalkyl and cycloalkenyl. Unless otherwise specified, these groups contain from 1 to 20 carbon atoms, with alkenyl groups containing from 2 to 20 carbon atoms, and alkynyl groups containing from 2 to 20 carbon atoms. In some embodiments, these groups have a

total of up to 10 carbon atoms, up to 8 carbon atoms, up to 6 carbon atoms, or up to 4 carbon atoms. Cyclic groups can be monocyclic or polycyclic and preferably have from 3 to 10 ring carbon atoms. Exemplary cyclic groups include cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclohexyl, adamantyl, and substituted and unsubstituted bornyl, norbornyl, and norbornenyl.

Unless otherwise specified, "alkylene", "alkenylene", and "alkynylene" are the divalent forms of the "alkyl", "alkenyl", and "alkynyl" groups defined above. The terms, "alkylenyl", "alkenylenyl", and "alkynylenyl" are use when "alkylene", "alkenylene", and "alkynylene", respectively, are substituted. For example, an arylalkylenyl group comprises an alkylene moiety to which an aryl group is attached.

The term "haloalkyl" is inclusive of groups that are substituted by one or more halogen atoms, including perfluorinated groups. This is also true of other groups that include the prefix "halo-". Examples of suitable haloalkyl groups are chloromethyl, trifluoromethyl, and the like.

The term "aryl" as used herein includes carbocyclic aromatic rings or ring systems. Examples of aryl groups include phenyl, naphthyl, biphenyl, fluorenyl and indenyl.

Unless otherwise indicated, the term "heteroatom" refers to the atoms O, S, or N.

The term "heteroaryl" includes aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N). Suitable heteroaryl groups include furyl, thienyl, pyridyl, quinolinyl, isoquinolinyl, indolyl, isoindolyl, triazolyl, pyrrolyl, tetrazolyl, imidazolyl, pyrazolyl, oxazolyl, thiazolyl, benzofuranyl, benzothiophenyl, carbazolyl, benzoxazolyl, pyrimidinyl, benzimidazolyl, quinoxalinyl, benzothiazolyl, naphthyridinyl, isoxazolyl, isothiazolyl, purinyl, quinazolinyl, pyrazinyl, 1-oxidopyridyl, pyridazinyl, triazinyl, tetrazinyl, oxadiazolyl, thiadiazolyl, and so on.

The term "heterocyclyl" includes non-aromatic rings or ring systems that contain at least one ring heteroatom (e.g., O, S, N) and includes all of the fully saturated and partially unsaturated derivatives of the above mentioned heteroaryl groups. Exemplary heterocyclic groups include pyrrolidinyl, tetrahydrofuranyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, thiazolidinyl, imidazolidinyl, isothiazolidinyl, tetrahydropyranyl, quinuclidinyl, homopiperidinyl (azepanyl), homopiperazinyl (diazepanyl), 1,3-dioxolanyl, aziridinyl, dihydroisoquinolin-(1*H*)-yl, octahydroisoquinolin-(1*H*)-yl, dihydroquinolin-

(2*H*)-yl, octahydroquinolin-(2*H*)-yl, dihydro-1*H*-imidazolyl, and the like. When "heterocyclyl" contains a nitrogen atom, the point of attachment of the heterocyclyl group may be the nitrogen atom.

The terms "arylene," "heteroarylene," and "heterocyclylene" are the divalent forms of the "aryl," "heteroaryl," and "heterocyclyl" groups defined above. The terms, "arylenyl", "heteroarylenyl", and "heterocyclylenyl" are used when "arylene," "heteroarylene," and "heterocyclylene", respectively, are substituted. For example, an alkylarylenyl group comprises an arylene moiety to which an alkyl group is attached.

When a group (or substituent or variable) is present more than once in any Formula described herein, each group (or substituent or variable) is independently selected, whether explicitly stated or not. For example, for the formula $-C(O)-N(R_8)_2$ each R_8 group is independently selected. In another example, when an R_1 and an R_3 group both contain an R_4 group, each R_4 group is independently selected. In a further example, when more than one Y group is present (i.e., R_1 and R_3 both contain a Y group) and each Y group contains one or more R_7 groups, then each Y group is independently selected, and each R_7 group is independently selected.

The invention is inclusive of the compounds described herein in any of their pharmaceutically acceptable forms, including isomers (e.g., diastereomers and enantiomers), salts, solvates, polymorphs, and the like. In particular, if a compound is optically active, the invention specifically includes each of the compound's enantiomers as well as racemic mixtures of the enantiomers. It should be understood that the term "compound" includes any or all of such forms, whether explicitly stated or not (although at times, "salts" are explicitly stated).

For any of the compounds presented herein, each one of the following variables (e.g., R, R', R'", R_A, R_B, R_{A1}, R_{B1}, R_1, R_2, R_{2a}, R_3, n, X, Y, Y', Z and so on) in any of its embodiments can be combined with any one or more of the other variables in any of their embodiments and associated with any one of the formulas described herein, as would be understood by one of skill in the art. Each of the resulting combinations of variables is an embodiment of the present invention.

In some embodiments, R is selected from the group consisting of halogen, hydroxy, alkyl, alkenyl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$. In certain embodiments, R is selected from the group consisting of halogen and hydroxy.

In some embodiments, R_A and R_B are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$. Alternatively, when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R''' groups. Alternatively, when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups.

In some embodiments, particularly embodiments of Formula I, R_A and R_B are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$.

In some embodiments, particularly embodiments of Formula I, R_A and R_B form a fused aryl or heteroaryl ring.

In some embodiments, particularly embodiments of Formula I, R_A and R_B form a fused 5 to 7 membered saturated ring.

In some embodiments, R_{A1} and R_{B1} are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$. Alternatively, R_{A1} and R_{B1} form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group. Alternatively, when taken together, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups.

In some embodiments, particularly embodiments of Formula II, R_{A1} and R_{B1} form a fused benzene ring which is unsubstituted.

In some embodiments, particularly embodiments of Formula II, R_{A1} and R_{B1} form a fused pyridine ring which is unsubstituted.

In some embodiments, particularly embodiments of Formula II, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, wherein the ring is unsubstituted.

In some embodiments, R_{A2} and R_{B2} are each independently selected from the group consisting of hydrogen, halogen, alkyl, alkenyl, alkoxy, alkylthio, and $-N(R_9)_2$. In certain of these embodiments, R_{A2} and R_{B2} are each independently alkyl. In some embodiments, R_{A2} and R_{B2} are each methyl.

In some embodiments, R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms. In certain embodiments, at least one of R_c or R_d is aryl.

In some embodiments, R_1 is selected from the group consisting of $-R_4$, $-X'-R_4$, $-X'-Y-R_4$, $-X'-Y-X'-Y-R_4$, $-X'-R_5$, $-X''-O-NR_{1a}-Y'-R_{1b}$, and $-X''-O-N=C(R_1')(R_1'')$. In some embodiments, R_1 is selected from the group consisting of $-R_4$, $-X'-R_4$, $-X'-Y-R_4$, $-X'-Y-X'-Y-R_4$, $-X'-R_5$, $-X''-O-NH-Y'-R_1'$, and $-X''-O-N=C(R_1')(R_1'')$.

In some emdobiments, R_1 is selected from the group consisting of alkyl, arylalkylenyl, aryloxyalkylenyl, hydroxyalkyl, alkylsulfonylalkylenyl, $-X'-Y-R_4$, and $-X'-R_5$. In some embodiments, R_1 is 2-methylpropyl, 2-hydroxy-2-methylpropyl, or $-X'-Y-R_4$. In some embodiments, R_1 is 2-methylpropyl or $-X'-Y-R_4$. In some embodiments, R_1 is 2-methylpropyl or 2-hydroxy-2-methylpropyl. In some embodiments, R_1 is 2-methyl-2-[(methylsulfonyl)amino]propyl or 4-[(methylsulfonyl)amino]butyl.

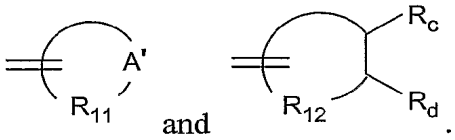
In some embodiments, R' is hydrogen or a non-interfering substituent. In some embodiments, R' is selected from the group consisting of $-R_4$, $-X'-R_4$, $-X'-Y-R_4$, $-X'-Y-X'-Y-R_4$, $-X'-R_5$, $-X''-O-NH-Y'-R_1'$, and $-X''-O-N=C(R_1')(R_1'')$. In some embodiments, R' is selected from the group consisting of $-R_4$, $-X'-R_4$, $-X'-Y-R_4$, $-X'-Y-X'-Y-R_4$, $-X'-R_5$, $-X''-O-NR_{1a}-Y'-R_{1b}$, and $-X''-O-N=C(R_1')(R_1'')$.

In some embodiments, R_1' and R_1'' are independently the same as R_2.

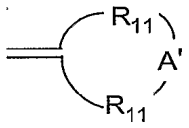
In some embodiments, R_1' and R_1'' are independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl,

heterocyclyl, heterocyclylalkylenyl, as well as alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of hydroxy, alkyl, haloalkyl, hydroxyalkyl, alkoxy, dialkylamino, -S(O)$_{0-2}$-alkyl, -S(O)$_{0-2}$-aryl, -NH-S(O)$_2$-alkyl, -NH-S(O)$_2$-aryl, haloalkoxy, halogen, cyano, nitro, aryl, heteroaryl, heterocyclyl, aryloxy, arylalkyleneoxy, -C(O)-O-alkyl, -C(O)-N(R_8)$_2$, -N(R_8)-C(O)-alkyl, -O-(CO)-alkyl, and -C(O)-alkyl.

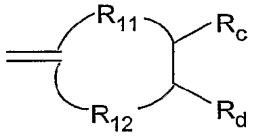
In some embodiments, R_1' and R_1" can join together to form a ring system selected from the group consisting of:



Alternatively, R_1' and R_1" can join together to form a ring system selected from the group consisting of:

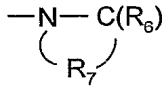


wherein the total number of atoms in the ring is 4 to 9, and

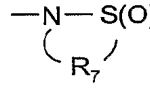


wherein the total number of atoms in the ring is 4 to 9.

In some embodiments, R_{1a} and R_{1b} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, heterocyclylalkylenyl, as well as alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of hydroxy, alkyl, haloalkyl, hydroxyalkyl, alkoxy, dialkylamino, -S(O)$_{0-2}$-alkyl, -S(O)$_{0-2}$-aryl, -NH-S(O)$_2$-alkyl, -NH-S(O)$_2$-aryl, haloalkoxy, halogen, cyano, nitro, aryl, heteroaryl, heterocyclyl, aryloxy, arylalkyleneoxy, -C(O)-O-alkyl, -C(O)-N(R_8)$_2$, -N(R_8)-C(O)-alkyl, -O-(CO)-alkyl, and -C(O)-alkyl. Alternatively, R_{1a} and R_{1b} together with the nitrogen atom and Y' to which they are bonded can join to form a ring selected from the group consisting of



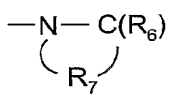
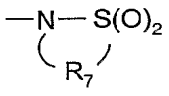
and



. In some embodiments, R_{1a} is hydrogen.

In some embodiments, R_2 and R_{2a} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, heterocyclylalkylenyl, as well as alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of hydroxy (i.e., hydroxyl), alkyl, haloalkyl, hydroxyalkyl, alkoxy, dialkylamino, -S(O)$_{0-2}$-alkyl, -S(O)$_{0-2}$-aryl, -NH-S(O)$_2$-alkyl, -NH-S(O)$_2$-aryl, haloalkoxy, halogen, cyano (i.e., nitrile), nitro, aryl, heteroaryl, heterocyclyl, aryloxy, arylalkyleneoxy, -C(O)-O-alkyl, -C(O)-N(R_8)$_2$, -N(R_8)-C(O)-alkyl, -O-(CO)-alkyl, and -C(O)-alkyl. Herein, this list of substituents is being referenced when an R_2 or R_{2a} group is referred to as substituted or optionally substituted.

Alternatively, R_2 and R_{2a} together with the nitrogen atom and Y' to which they are bonded can join to form a ring selected from the group consisting of

 and  .

In some embodiments, particularly embodiments of Formulas IIIa and IVa, R_2 and R_{2a} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, heteroaryl, wherein the alkyl, alkenyl, aryl, and heteroaryl are each optionally substituted with one or more substitutents selected from the group consisting of C_{1-10} alkyl, aryl, heteroaryl, C_{1-10} alkoxy, -O-C(O)-C_{1-10} alkyl, -C(O)-O-C_{1-10} alkyl, halogen, and cyano (i.e., nitrile).

In some embodiments, R_2 is alkyl or substituted alkyl. In some embodiments, R_2 is methyl or cyclopropyl.

In some embodiments, R_2 is alkenyl or substituted alkenyl. In some embodiments, R_2 is aryl, arylalkylenyl, substituted aryl, or substituted arylalkylenyl. In some embodiments, R_2 is heteroaryl , heteroarylalkylenyl, substituted heteroaryl, or substituted heteroarylalkylenyl. In some embodiments, R_2 is heterocyclyl, heterocyclylalkylenyl, substituted heterocyclyl, or substituted heterocyclylalkylenyl.

In some embodiments, R_2 is selected from the group consisting of methyl, (ethoxycarbonyl)methyl, ethyl, cyclopropyl, cyclopropylmethyl, 2-(ethoxycarbonyl)cyclopropylmethyl, propyl, butyl, 2-methylpropyl, *tert*-butyl, 3-

methylbutyl, 2,2-dimethylpropyl, cyclopentyl, 2-cyclopentylethyl, furyl, fur-3-ylmethyl, furfuryl, furfurylmethyl, cyclohexyl, tetrahydrofuranyl, tetrahydrofuran-3-ylmethyl, 2-(methylthio)ethyl, 3-(methylthio)propyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,6-dimethoxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-(dimethylamino)phenyl, 3-hydroxy-4-methoxyphenyl, 4-acetamidophenyl, 4-(methoxycarbonyl)phenyl, 4-(trifluoromethyl)phenyl, biphenyl, benzyl, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2-cyanobenzyl, 3-cyanobenzyl, 4-cyanobenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 4-dimethylaminobenzyl, 3-hydroxy-4-methoxybenzyl, 4-acetamidobenzyl, 4-(methoxycarbonyl)benzyl, 4-(trifluoromethyl)benzyl, 1-phenylethyl, 2-phenylethyl, 2-phenylpropyl, 3-phenylpropyl, 2-phenylethenyl, phenoxymethyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethy, 1-methylpyrrol-2-yl, 1-methylpyrrol-2-ylmethyl, 1-methylimidazol-2-yl, 1-methylimidazol-2-ylmethyl, 1-methylimidazol-4-yl, 1-methylimidazol-4-ylmethyl, 3-cyclohexen-1-yl, 3-cyclohexen-1-ylmethyl, 3,4-dihydro-2*H*-pyran-2-yl, 3,4-dihydro-2*H*-pyran-2-ylmethyl, 1-methylpiperidin-4-yl, 1-acetylpiperidin-4-yl, 1-benzylpiperidin-4-yl, 2-thienyl, 3-thienyl, thien-2-ylmethyl, thiazol-2-yl, thiazol-2-ylmethyl, 5-isoxazolyl, 5-isoxazolylmethyl, quinolin-2-yl, quinolin-2-ylmethyl, pyrrolidinyl, 3,4-dichlorophenyl, α-methylbenzyl, methoxymethyl, trifluoromethyl, and 2,2,2-trifluoroethyl.

In some embodiments, R_2 is selected from the group consisting of methyl, (ethoxycarbonyl)methyl, ethyl, cyclopropyl, cyclopropylmethyl, 2-(ethoxycarbonyl)cyclopropylmethyl, propyl, butyl, 2-methylpropyl, *tert*-butyl, 3-methylbutyl, 2,2-dimethylpropyl, cyclopentyl, 2-cyclopentylethyl, furyl, fur-3-ylmethyl, furfuryl, furfurylmethyl, cyclohexyl, tetrahydrofuranyl, tetrahydrofuran-3-ylmethyl, 2-(methylthio)ethyl, 3-(methylthio)propyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,6-dimethoxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-

(dimethylamino)phenyl, 3-hydroxy-4-methoxyphenyl, 4-acetamidophenyl, 4-(methoxycarbonyl)phenyl, 4-(trifluoromethyl)phenyl, biphenyl, benzyl, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2-cyanobenzyl, 3-cyanobenzyl, 4-cyanobenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 4-dimethylaminobenzyl, 3-hydroxy-4-methoxybenzyl, 4-acetamidobenzyl, 4-(methoxycarbonyl)benzyl, 4-(trifluoromethyl)benzyl, 1-phenylethyl, 2-phenylethyl, 2-phenylpropyl, 3-phenylpropyl, 2-phenylethenyl, phenoxymethyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethy, 1-methylpyrrol-2-yl, 1-methylpyrrol-2-ylmethyl, 1-methylimidazol-2-yl, 1-methylimidazol-2-ylmethyl, 1-methylimidazol-4-yl, 1-methylimidazol-4-ylmethyl, 3-cyclohexen-1-yl, 3-cyclohexen-1-ylmethyl, 3,4-dihydro-2*H*-pyran-2-yl, 3,4-dihydro-2*H*-pyran-2-ylmethyl, 1-methylpiperidin-4-yl, 1-acetylpiperidin-4-yl, 1-benzylpiperidin-4-yl, 2-thienyl, 3-thienyl, thien-2-ylmethyl, thiazol-2-yl, thiazol-2-ylmethyl, 5-isoxazolyl, 5-isoxazolylmethyl, quinolin-2-yl, quinolin-2-ylmethyl, and pyrrolidinyl.

In some embodiments, particularly embodiments of Formulas IIIa and IVa, R_{2a} is hydrogen.

In some embodiments, R''' is a non-interfering substituent. In some embodiments, R''' is R_3. In some embodiments, particularly embodiments of Formula III, R''' is R or R_3 when n is 1, R or one R and one R_3 when n is 2, or R when n is 3 to 4.

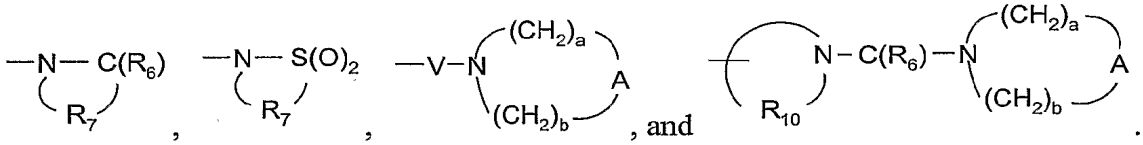
In some embodiments, R_3 is selected from the group consisting of -Z-R_4, -Z-X'-R_4, -Z-X'-Y-R_4, -Z-X'-Y-X'-Y-R_4, and -Z-X'-R_5. In some embodiments, R_3 is selected from the group consisting of -Z-R_4 and -Z-X'-Y-R_4.

In some embodiments, R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy,

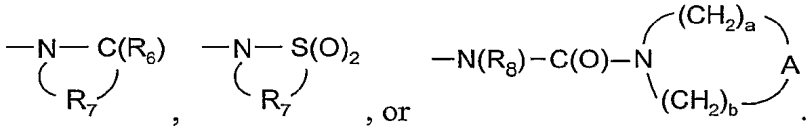
heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo.

In some embodiments, R_4 is hydrogen, alkyl, alkenyl, aryl, or heteroaryl. In some embodiments, R_4 is hydrogen, alkyl, alkenyl, aryl, or heteroaryl, wherein alkyl and alkenyl are optionally substituted by aryl or aryloxy and wherein aryl is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, cyano, haloalkyl, and halogen. In some embodiments, R_4 is selected from the group consisting of aryl or heteroaryl, each of which may be unsubstituted or substituted by one or more substituents selected from the group consisting of alkyl, hydroxy, cyano, hydroxyalkyl, dialkylamino, and alkoxy.

In some embodiments, R_5 is selected from the group consisting of



In some embodiments, R_5 is



In some embodiments, R_6 is selected from the group consisting of =O and =S. In some embodiments, R_6 is =O.

In some embodiments, R_7 is C_{2-7} alkylene. In some embodiments, R_7 is ethylene. In some embodiments, R_7 is propylene.

In some embodiments, R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl. In some embodiments, R_8 is hydrogen or methyl. In some embodiments, R_8 is hydrogen.

In some embodiments, R_9 is selected from the group consisting of hydrogen and alkyl.

In some embodiments, R_{10} is C_{3-8} alkylene. In some embodiments, R_{10} is pentylene.

In some embodiments, R_{11} is C_{3-9} alkylene or C_{3-9} alkenylene, optionally interrupted by one hetero atom. In some embodiments, R_{11} is C_{1-6} alkylene or

C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom. In some embodiments, R_{11} is methylene; in some embodiments, R_{11} is ethylene.

In some embodiments, R_{12} is C_{2-7} alkylene or C_{2-7} alkenylene, optionally interrupted by one hetero atom. In some embodiments, R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom. In some embodiments, R_{12} is ethylene.

In some embodiments, R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups. In some embodiments, R_{13} is hydrogen.

In some embodiments, A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$. In some embodiments, A is selected from the group consisting of $-CH_2-$ and -O-.

In some embodiments, A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$. In some embodiments, A' is $-CH_2-$, -O-, or $-N(-Q-R_4)-$.

In some embodiments, Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$. In some embodiments, Q is selected from the group consisting of -C(O)-, $-S(O)_2-$, and $-C(O)-N(R_8)-W-$.

In some embodiments, V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$. In some embodiments, V is $-N(R_8)-C(O)-$.

In some embodiments, W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$. In some embodiments, W is selected from the group consisting of a bond and -C(O)-.

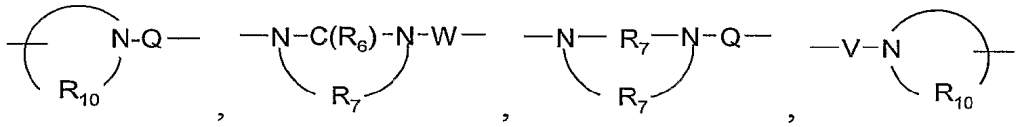
In some embodiments, X is C_{1-10} alkylene or C_{2-10} alkenylene. Preferably, X is C_{1-10} alkylene or C_{3-10} alkenylene. In some embodiments, particularly embodiments of Formulas IIIa and IVa, X is C_{1-4} alkylene. In some embodiments, X is methylene.

In some embodiments, X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups. In

some embodiments, X' is alkylene. In some embodiments, X' is ethylene, propylene, or butylene (including isobutylene).

In some embodiments, X" is $-CH(R_{13})$-alkylene- or $-CH(R_{13})$-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups. In some embodiments, particularly in embodiments of Formula IIIa and IVa, X" is $-CH(R_{13})$-alkylene- or $-CH(R_{13})$-alkenylene-.

In some embodiments, Y is selected from the group consisting of $-S(O)_{0-2}$-, $-S(O)_2-N(R_8)$-, $-C(R_6)$-, $-C(R_6)-O$-, $-O-C(R_6)$-, $-O-C(O)-O$-, $-N(R_8)-Q$-, $-C(R_6)-N(R_8)$-, $-O-C(R_6)-N(R_8)$-, $-C(R_6)-N(OR_9)$-,



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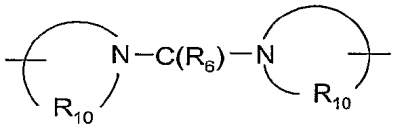

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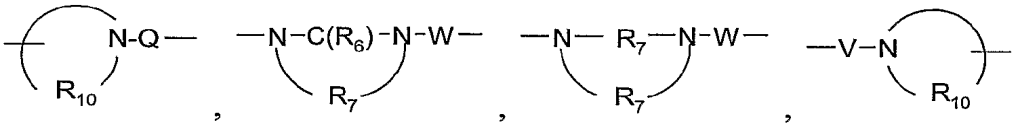
In some embodiments, Y is selected from the group consisting of $-S(O)_{0-2}$-, $-S(O)_2-N(R_8)$-, $-C(R_6)$-, $-C(R_6)-O$-, $-O-C(R_6)$-, $-O-C(O)-O$-, $-N(R_8)-Q$-, $-C(R_6)-N(R_8)$-, $-O-C(R_6)-N(R_8)$-, $-C(R_6)-N(OR_9)$-,



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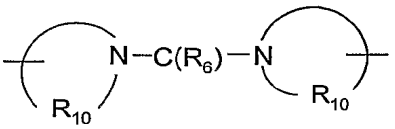

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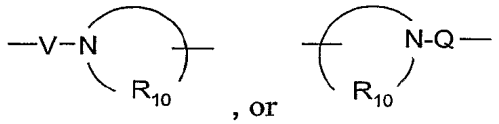
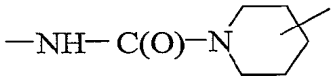
In some embodiments, Y is $-N(R_8)-C(O)$-, $-N(R_8)-S(O)_2$-, $-N(R_8)-S(O)_2-N(R_8)$-, $-N(R_8)-C(O)-N(R_8)$-, $-N(R_8)-C(O)-N(R_8)-C(O)$-,

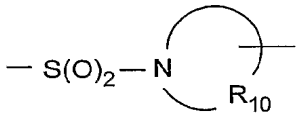


, or .

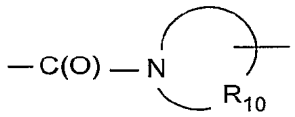
In some embodiments, Y is $-NH-C(O)$-, $-NH-S(O)_2$-, $-NH-S(O)_2-N(R_8)$-, $-NH-C(O)-N(R_8)$-, $-NH-C(O)-NH-C(O)$-, or



In some embodiments, Y' is selected from the group consisting of a bond, -C(O)-, -C(S)-, -$S(O)_2$-, -$S(O)_2$-N(R_8)-,

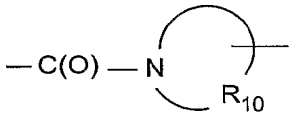


-C(O)-O-, -C(O)-N(R_8)-, -C(S)-N(R_8)-, -C(O)-N(R_8)-$S(O)_2$-, -C(O)-N(R_8)-C(O)-, -C(S)-N(R_8)-C(O)-,



, -C(O)-C(O)-, -C(O)-C(O)-O-, and -C(=NH)-N(R_8)-.

In some embodiments, Y' is selected from the group consisting of a bond, -C(O)-, -C(O)-O-, -$S(O)_2$-, -$S(O)_2$-N(R_8)-, -C(O)-N(R_8)-, -C(S)-N(R_8)-, -C(O)-N(R_8)-C(O)-, and



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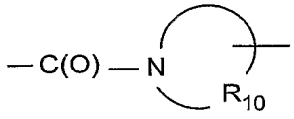
In some embodiments, particularly embodiments of Formulas IIIa and IVa, Y' is selected from the group consisting of a bond, -C(O)-, -C(O)-O-, -$S(O)_2$-, -$S(O)_2$-N(R_8)-, -C(O)-N(R_8)-, -C(O)-N(R_8)-C(O)-, and



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In some embodiments, Y' is selected from the group consisting of -C(O)-, -$S(O)_2$-, and -C(O)-N(R_8)-.

In some embodiments, Z is a bond or -O-. In some embodiments, Z is a bond. In some embodiments, Z is –O-.

In some embodiments, a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7. In some embodiments, a and b are each 2.

In some embodiments, n is an integer from 0 to 4. In some embodiments, n is 0 or 1. In some embodiments, particularly embodiments of Formula IVa, n is 0.

In some embodiments, m is 0 or 1. In some embodiments m is 1. In some embodiments, m is 0.

In some embodiments, m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1.

In some embodiments, particularly embodiments of Formula IIIa, m and n are 0. In some embodiments, n is 0 or m is 0.

In some embodiments, p is an integer from 0 to 3. In some embodiments, p is 0 or 1. In some embodiments, p is 0.

In some embodiments, m is 0 or 1, with the proviso that when m is 1, p is 0 or 1.

In some embodiments, p and m are 0.

In some embodiments, particularly embodiments of Formula III, R' is selected from the group consisting of:

$-R_4$,

$-X'-R_4$,

$-X'-Y-R_4$,

$-X'-Y-X'-Y-R_4$,

$-X'-R_5$,

$-X''-O-NH-Y'-R_1'$, and

$-X''-O-N=C(R_1')(R_1'')$;

wherein X', X", Y, Y', R_1', R_1'', R_4, and R_5, are as defined above.

In some embodiments, particularly embodiments of Formula III, R"' is R or R_3 when n is 1, R or one R and one R_3 when n is 2, or R when n is 3 to 4;

wherein:

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X'-R_4$,

$-Z-X'-Y-R_4$,

$-Z-X'-Y-X'-Y-R_4$, and

$-Z-X'-R_5$;

n is an integer from 0 to 4;

Z is a bond or -O-; and

X', Y, R_4, R_5, and R_9 are as defined above.

In some embodiments, particularly embodiments of Formulas IIIa and IVa, R_2 is alkyl or substituted alkyl, and R_{2a} is hydrogen.

In some embodiments, R_2 is methyl or cyclopropyl, and R_{2a} is hydrogen.

In some embodiments, particularly embodiments of Formulas IIIa and IVa, R_2 is alkenyl or substituted alkenyl, and R_{2a} is hydrogen.

In some embodiments, particularly embodiments of Formulas IIIa and IVa, R_2 is aryl, arylalkylenyl, substituted aryl, or substituted arylalkylenyl, and R_{2a} is hydrogen.

In some embodiments, particularly embodiments of Formulas IIIa and IVa, R_2 is heteroaryl, heteroarylalkylenyl, substituted heteroaryl, or substituted heteroarylalkylenyl, and R_{2a} is hydrogen.

In some embodiments, particularly embodiments of Formulas IIIa and IVa, R_2 is heterocyclyl, heterocyclylalkylenyl, substituted heterocyclyl, or substituted heterocyclylalkylenyl, and R_{2a} is hydrogen.

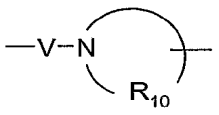
In some embodiments, R_2 is selected from the group consisting of methyl, (ethoxycarbonyl)methyl, ethyl, cyclopropyl, cyclopropylmethyl, 2-(ethoxycarbonyl)cyclopropylmethyl, propyl, butyl, 2-methylpropyl, *tert*-butyl, 3-methylbutyl, 2,2-dimethylpropyl, cyclopentyl, 2-cyclopentylethyl, furyl, fur-3-ylmethyl, furfuryl, furfurylmethyl, cyclohexyl, tetrahydrofuranyl, tetrahydrofuran-3-ylmethyl, 2-(methylthio)ethyl, 3-(methylthio)propyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,6-dimethoxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-

fluorophenyl, 4-fluorophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-(dimethylamino)phenyl, 3-hydroxy-4-methoxyphenyl, 4-acetamidophenyl, 4-(methoxycarbonyl)phenyl, 4-(trifluoromethyl)phenyl, biphenyl, benzyl, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2-cyanobenzyl, 3-cyanobenzyl, 4-cyanobenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 4-dimethylaminobenzyl, 3-hydroxy-4-methoxybenzyl, 4-acetamidobenzyl, 4-(methoxycarbonyl)benzyl, 4-(trifluoromethyl)benzyl, 1-phenylethyl, 2-phenylethyl, 2-phenylpropyl, 3-phenylpropyl, 2-phenylethenyl, phenoxymethyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethy, 1-methylpyrrol-2-yl, 1-methylpyrrol-2-ylmethyl, 1-methylimidazol-2-yl, 1-methylimidazol-2-ylmethyl, 1-methylimidazol-4-yl, 1-methylimidazol-4-ylmethyl, 3-cyclohexen-1-yl, 3-cyclohexen-1-ylmethyl, 3,4-dihydro-2*H*-pyran-2-yl, 3,4-dihydro-2*H*-pyran-2-ylmethyl, 1-methylpiperidin-4-yl, 1-acetylpiperidin-4-yl, 1-benzylpiperidin-4-yl, 2-thienyl, 3-thienyl, thien-2-ylmethyl, thiazol-2-yl, thiazol-2-ylmethyl, 5-isoxazolyl, 5-isoxazolylmethyl, quinolin-2-yl, quinolin-2-ylmethyl, pyrrolidinyl, 3,4-dichlorophenyl, α-methylbenzyl, methoxymethyl, trifluoromethyl, and 2,2,2-trifluoroethyl; and R_{2a} is hydrogen.

In some embodiments, particularly embodiments of Formulas IIIa and IVa, R_2 is selected from the group consisting of methyl, (ethoxycarbonyl)methyl, ethyl, cyclopropyl, cyclopropylmethyl, 2-(ethoxycarbonyl)cyclopropylmethyl, propyl, butyl, 2-methylpropyl, *tert*-butyl, 3-methylbutyl, 2,2-dimethylpropyl, cyclopentyl, 2-cyclopentylethyl, furyl, fur-3-ylmethyl, furfuryl, furfurylmethyl, cyclohexyl, tetrahydrofuranyl, tetrahydrofuran-3-ylmethyl, 2-(methylthio)ethyl, 2-(methylthio)propyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,6-dimethoxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-(dimethylamino)phenyl, 3-hydroxy-4-methoxyphenyl, 4-acetamidophenyl, 4-(methoxycarbonyl)phenyl, 4-(trifluoromethyl)phenyl, biphenyl, benzyl, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2-cyanobenzyl, 3-cyanobenzyl, 4-cyanobenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 4-

dimethylaminobenzyl, 3-hydroxy-4-methoxybenzyl, 4-acetamidobenzyl, 4-(methoxycarbonyl)benzyl, 4-(trifluoromethyl)benzyl, 1-phenylethyl, 2-phenylethyl, 2-phenylpropyl, 3-phenylpropyl, 2-phenylethenyl, phenoxymethyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethy, 1-methylpyrrol-2-yl, 1-methylpyrrol-2-ylmethyl, 1-methylimidazol-2-yl, 1-methylimidazol-2-ylmethyl, 1-methylimidazol-4-yl, 1-methylimidazol-4-ylmethyl, 3-cyclohexen-1-yl, 3-cyclohexen-1-ylmethyl, 3,4-dihydro-2*H*-pyran-2-yl, 3,4-dihydro-2*H*-pyran-2-ylmethyl, 1-methylpiperidin-4-yl, 1-acetylpiperidin-4-yl, 1-benzylpiperidin-4-yl, 2-thienyl, 3-thienyl, thien-2-ylmethyl, thiazol-2-yl, thiazol-2-ylmethyl, 5-isoxazolyl, 5-isoxazolylmethyl, quinolin-2-yl, quinolin-2-ylmethyl, and pyrrolidinyl; and R_{2a} is hydrogen.

In some embodiments of Formulas IIIa and IVa, R_1 is selected from the group consisting of alkyl, arylalkylenyl, aryloxyalkylenyl, hydroxyalkyl, alkylsulfonylalkylenyl, -X'-Y-R_4, and -X'-R_5; wherein X' is alkylene; Y is -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-S(O)$_2$-N(R_8)-, -N(R_8)-C(O)-N(R_8)-, -N(R_8)-C(O)-N(R_8)-C(O)-,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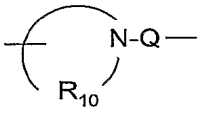
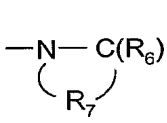

; R_4 is hydrogen, alkyl, alkenyl, aryl, or heteroaryl; and R_5 is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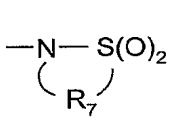
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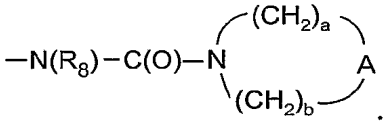
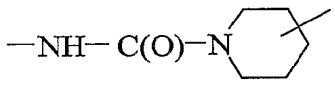
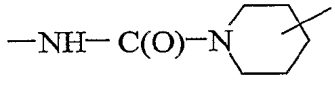

.

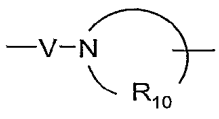
In some embodiments, R_1 is 2-methylpropyl or –X'-Y-R_4; X' is ethylene, propylene, or butylene; Y is -NH-C(O)-, -NH-S(O)$_2$-, -NH-S(O)$_2$-N(R_8)-, -NH-C(O)-N(R_8)-, -NH-C(O)-NH-C(O)-, or

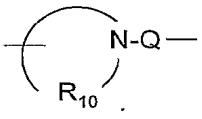

; and R_8 is hydrogen or methyl.

In some embodiments, R_1 is 2-methylpropyl, 2-hydroxy-2-methylpropyl, or –X'-Y-R_4; X' is ethylene, propylene, or butylene (including isobutylene); Y is -NH-C(O)-, -NH-S(O)$_2$-, -NH-S(O)$_2$-N(R_8)-, -NH-C(O)-N(R_8)-, -NH-C(O)-NH-C(O)-, or

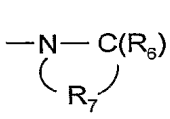

; and R_8 is hydrogen or methyl.

In some embodiments, R_1 is selected from the group consisting of alkyl, arylalkylenyl, aryloxyalkylenyl, hydroxyalkyl, alkylsulfonylalkylenyl, -X'-Y-R_4, and -X'-R_5; wherein X' is alkylene; Y is -N(R_8)-C(O)-, -N(R_8)-S(O)$_2$-, -N(R_8)-S(O)$_2$-N(R_8)-, -N(R_8)-C(O)-N(R_8)-, -N(R_8)-C(O)-N(R_8)-C(O)-,



, or


; R_4 is hydrogen, alkyl, alkenyl, aryl, or heteroaryl, wherein alkyl and alkenyl are optionally substituted by aryl or aryloxy and wherein aryl is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, cyano, haloalkyl, and halogen; and R_5 is



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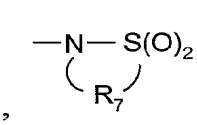
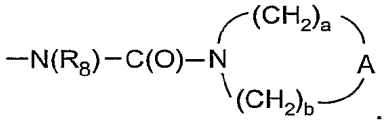
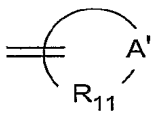
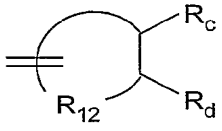


, or


.

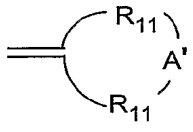
In some embodiments, R_1' and R_1" can join together to form a ring system selected from the group consisting of:



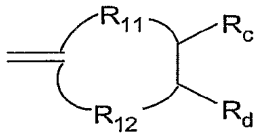
and


; wherein A' is selected from the group consisting of -O-, -S(O)$_{0-2}$-, -N(-Q-R_4)-, and -CH_2-; R_{11} is C_{3-9} alkylene or C_{3-9} alkenylene, optionally interrupted by one hetero atom; R_{12} is C_{2-7} alkylene or C_{2-7} alkenylene, optionally interrupted by one heteroatom; and R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and –N(R_9)$_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms.

Alternatively, R_1' and R_1" can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9; and further

wherein A' is selected from the group consisting of -O-, -$S(O)_{0-2}$-, -N(-Q-R_4)-, and -CH_2-; R_{11} is C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom; R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom; and R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and –$N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms.

Preparation of the Compounds

Compounds of the invention can be prepared according to Reaction Scheme I where R, R_1, X, and n are as defined above, Hal is chloro, bromo, or iodo, and R_2' and R_2" are the same as R_1' and R_1" as defined above. In step (1) of Reaction Scheme I, a quinoline-3,4-diamine of Formula X is reacted with a carboxylic acid or an equivalent thereof to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XI. Suitable equivalents to a carboxylic acid include orthoesters, and 1,1-dialkoxyalkyl alkanoates. The carboxylic acid or equivalent is selected such that it will provide the desired –X-Hal substituent in a compound of Formula XI. For example, Hal-X-CO_2H or Hal-X-C(O-alkyl)$_3$ will provide a compound with the desired –X-Hal substitutent at the 2-position. The reaction can be run in the absence of solvent or in an inert solvent such as toluene. The reaction is run with sufficient heating to drive off any alcohol or water formed as a byproduct of the reaction. Optionally a catalyst such as pyridine hydrochloride can be included.

Alternatively, step (1) can be carried out by (i) reacting a compound of Formula X with an acyl halide of formula Hal-X-C(O)Cl or Hal-X-C(O)Br and then (ii) cyclizing. In part (i) the acyl halide is added to a solution of a compound of Formula X in an inert solvent such as acetonitrile, pyridine or dichloromethane. The reaction can be carried out at ambient temperature. A catalyst such as pyridine hydrochloride can be included. Alternatively, the reaction can be carried out in the presence of triethylamine. In part (ii) the product of part (i) is heated in pyridine. The two steps can be combined into a single step when the reaction is run in pyridine or solvents such as dichloromethane or dichloroethane in the presence of triethylamine.

Many compounds of Formula X are known and can be readily prepared using known synthetic routes; see for example, U.S. Patent Nos. 4,689,338 (Gerster), 4,929,624 (Gerster et al.), 5,268,376 (Gerster), 5,389,640 (Gerster et al.), 6,331,539 (Crooks et al.), 6,451,810 (Coleman et al.), 6,541,485 (Crooks et al.), 6,660,747 (Crooks et al.), 6,670,372 (Charles et al.), 6,683,088 (Crooks et al.), 6,656,938 (Crooks et al.), and 6,664,264 (Dellaria et al.).

In step (2) of Reaction Scheme I a 1*H*-imidazo[4,5-*c*]quinoline of Formula XI is oxidized to provide an *N*-oxide of Formula XII using a conventional oxidizing agent that is capable of forming *N*-oxides. The reaction can be carried out by treating a solution of a compound of Formula XI in a suitable solvent such as chloroform or dichloromethane with 3-chloroperoxybenzoic acid at ambient temperature.

In step (3) of Reaction Scheme I an *N*-oxide of Formula XII is aminated to provide a 1*H*-imidazo[4,5-*c*]quinoline-4-amine of Formula XIII. The reaction is carried out in two parts. In part (i) a compound of Formula XII is reacted with an acylating agent. Suitable acylating agents include alkyl- or arylsulfonyl chorides (e.g., benzenesulfonyl choride, methanesulfonyl choride, or *p*-toluenesulfonyl chloride). In part (ii) the product of part (i) is reacted with an excess of an aminating agent. Suitable aminating agents include ammonia (e.g. in the form of ammonium hydroxide) and ammonium salts (e.g., ammonium carbonate, ammonium bicarbonate, ammonium phosphate). The reaction can be carried out by dissolving a compound of Formula XII in a suitable solvent such as dichloromethane or chloroform, adding ammonium hydroxide to the solution, and then adding *p*-toluenesulfonyl chloride. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (4) of Reaction Scheme I a 1*H*-imidazo[4,5-*c*]quinoline-4-amine of Formula XIII is treated with *N*-hydroxyphthalimide to provide an *N*-phthalimide-protected 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XIV. The reaction is conveniently carried out by adding a base, such as triethylamine, to a solution of *N*-hydroxyphthalimide in a suitable solvent such as *N,N*-dimethylformamide (DMF); and then adding the 1*H*-imidazo[4,5-*c*]quinoline-4-amine of Formula XIII in a suitable solvent (for example, DMF) to the resulting mixture. The reaction can be carried out at ambient

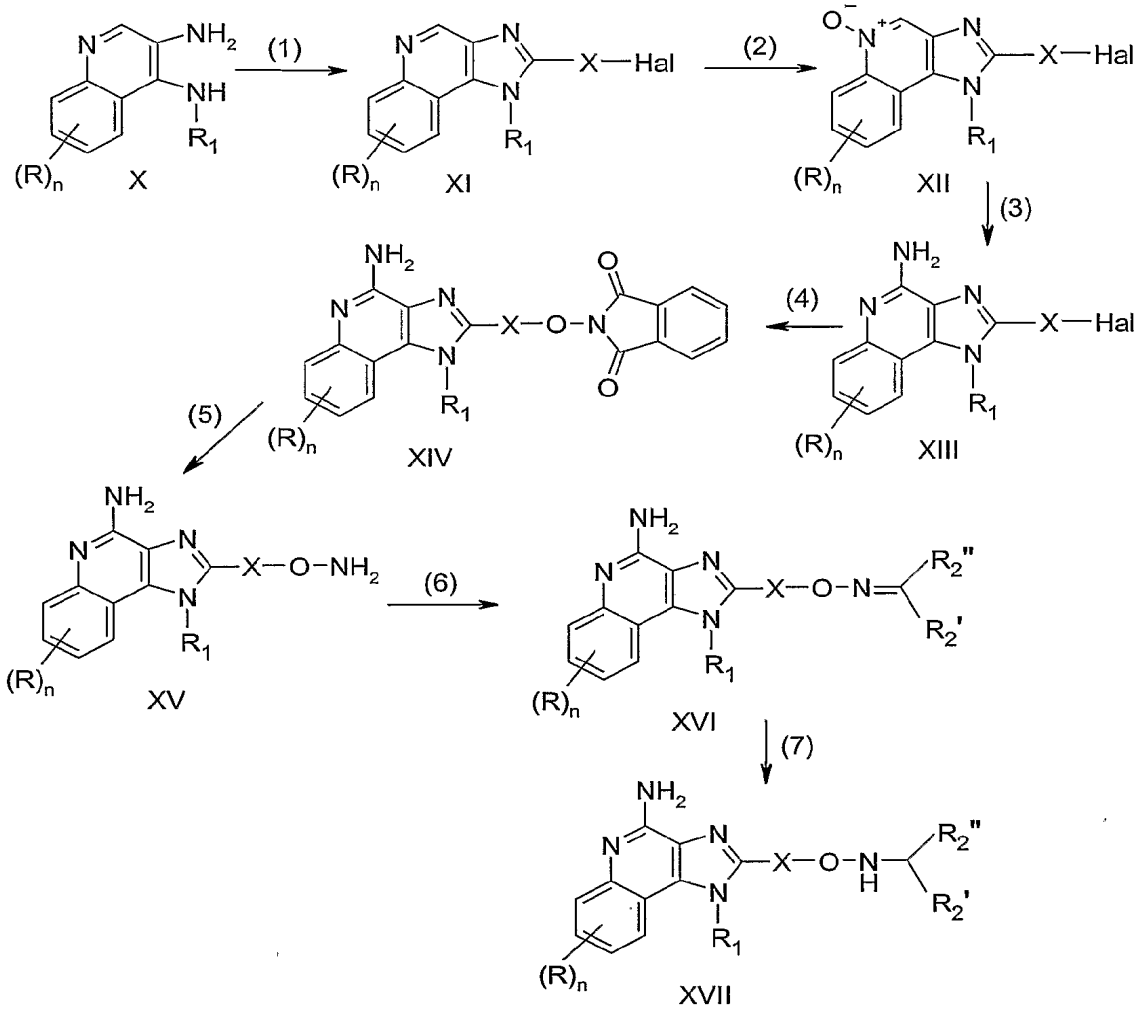
temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

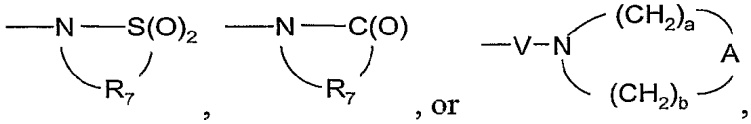
In step (5) of Reaction Scheme I an *N*-phthalimide-protected 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XIV is converted to a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XV. Removal of the *N*-phthalimide protecting group is conveniently carried out by adding hydrazine to a suspension of an *N*-phthalimide-protected 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XIV in a suitable solvent such as ethanol. The reaction can be carried out at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (6) of Reaction Scheme I a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XV is reacted with an aldehyde or ketone of formula $R_2'C(O)R_2''$ to provide a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XVI. Numerous aldehydes and ketones of formula $R_2'C(O)R_2''$ are commercially available; others can be readily prepared using known synthetic methods. The reaction can be conveniently carried out by adding the aldehyde or ketone of formula $R_2'C(O)R_2''$ to a 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XV in a suitable solvent such as methanol. The reaction can be carried out at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (7) of Reaction Scheme I a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XVI is reduced to provide a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XVII, which is a subgenus of Formulas I, II, III, and IIIa. The reduction is conveniently carried out by treating a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XVI with excess sodium cyanoborohydride in a suitable solvent or solvent mixture such as methanol/acetic acid. The reaction can be carried out at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme I



Compounds of the invention can be prepared according to Reaction Scheme II where R, R_4, R_8, Q, X, X', Hal, and n are as defined above, Boc is *tert*-butoxycarbonyl, R_{5a} is  , wherein V is $-N(R_8)-C(R_6)-$, and R_2' and R_2'' are the same as R_1' and R_1'' as defined above. In step (1) of Reaction Scheme II a 1*H*-imidazo[4,5-*c*]quinolin-1-yl *tert*-butylcarbamate of Formula XVIII is treated with *N*-hydroxyphthalimide to provide an *N*-phthalimide-protected 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XIX. The reaction is conveniently carried out by adding a base, such as triethylamine, to *N*-hydroxyphthalimide dissolved in

a suitable solvent such as DMF; and then adding the 1*H*-imidazo[4,5-*c*]quinolin-1-yl *tert*-butylcarbamate of Formula XVIII in a suitable solvent (for example, DMF) to the resulting mixture. The reaction can be carried out at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods. Compounds of Formula XVIII can be readily prepared using known synthetic routes; see for example, U.S. Patent No. 6,451,485 (Crooks et al.), and 6,660,747 (Crooks et al to prepare a quinoline-3,4-diamine that can be treated according to steps (1) to (3) of Reaction Scheme I.

In step (2) of Reaction Scheme II an *N*-phthalimide-protected 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XIX is converted to a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XX. Removal of the *N*-phthalimide protecting group is conveniently carried out by adding hydrazine to a suspension of an *N*-phthalimide-protected 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XIX in a suitable solvent such as ethanol. The reaction can be carried out at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

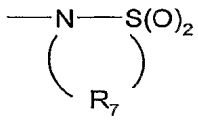
In step (3) of Reaction Scheme II a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XX is reacted with an aldehyde or ketone of formula $R_2'C(O)R_2''$ to provide a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XXI. Numerous aldehydes and ketones of formula $R_2'C(O)R_2''$ are commercially available; others can be readily prepared using known synthetic methods. The reaction can be conveniently carried out by adding the aldehyde or ketone of formula $R_2'C(O)R_2''$ to a solution of the 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula XX in a suitable solvent such as methanol. The reaction can be carried out at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (4) of Reaction Scheme II a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XXI is deprotected to provide an amino group at the 1-position of a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XXII. The reaction can be conveniently carried out by dissolving a compound of Formula XXI in a mixture of trifluoroacetic acid and a suitable solvent such as dichloromethane. The reaction can be carried out at ambient

temperature. The product or a pharmaceutically acceptable salt thereof, including the trifluoroacetate salt, can be isolated using conventional methods.

In steps (5) and (5a) of Reaction Scheme II a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XXII is converted to a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XXIII or XXIV, using conventional methods. For example, sulfonamides of Formula XXIII (Q is $-S(O)_2-$) can be prepared by reacting a compound of Formula XXII with a sulfonyl chloride of formula $R_4S(O)_2Cl$. The reaction can be carried out at ambient temperature in an inert solvent such as chloroform or dichloromethane by adding the sulfonyl chloride to a compound of Formula XXII in the presence of a base such as *N*,*N*-diisopropylethylamine, triethylamine, or pyridine. Sulfamides of Formula XXIII (Q is, for example, $-S(O)_2-N(R_8)-$) can be prepared by reacting a compound of Formula XXII with a sulfamoyl chloride of formula $R_4(R_8)NS(O)_2Cl$ or by reacting a compound of Formula XXII with sulfuryl chloride to generate a sulfamoyl chloride in situ, and then reacting the resulting sulfamoyl chloride with an amine of formula $HN(R_8)R_4$. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods. Some sulfamoyl chlorides of formula $R_4(R_8)NS(O)_2Cl$ and many sulfonyl chlorides of formula $R_4S(O)_2Cl$ and amines of formula $HN(R_8)R_4$ are commercially available; others can be prepared using known synthetic methods.

In another example, using step (5a) of Reaction Scheme II, a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XXII is reacted with a chloroalkanesulfonyl chloride of formula $Cl-R_7-S(O)_2Cl$ to provide a compound of Formula XXIV, wherein R_{5a} is a ring having the structure

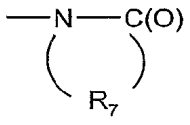


The reaction is preferably carried out by adding the chloroalkanesulfonyl chloride to a solution of a compound of Formula XXII in a suitable solvent such as dichloromethane in the presence of a base such as triethylamine. The intermediate chloroalkanesulfonamide may optionally be isolated before treatment with a stronger base such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at ambient temperature. If the intermediate chloroalkanesulfonamide is isolated, the reaction with DBU can be carried out in a suitable

solvent such as DMF. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Amides of Formulas XXIII (Q is, for example, -C(O)-) and XXIV can be prepared from 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XXII using conventional methods. For example, a compound of Formula XXII can be reacted with an acid chloride of formula $R_4C(O)Cl$ to provide a compound of Formula XXIII. The reaction can be carried out by adding the acid chloride to a solution of a compound of Formula XXII in a suitable solvent such as chloroform, optionally in the presence of a base such as *N*,*N*-diisopropylethylamine, triethylamine, or pyridine, at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In another example shown in step (5a), a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XXII is reacted with a chloroalkanoyl chloride compound of formula $Cl\text{-}R_7\text{-}C(O)Cl$ to provide a compound of Formula XXIV, wherein R_{5a} is a ring having the structure



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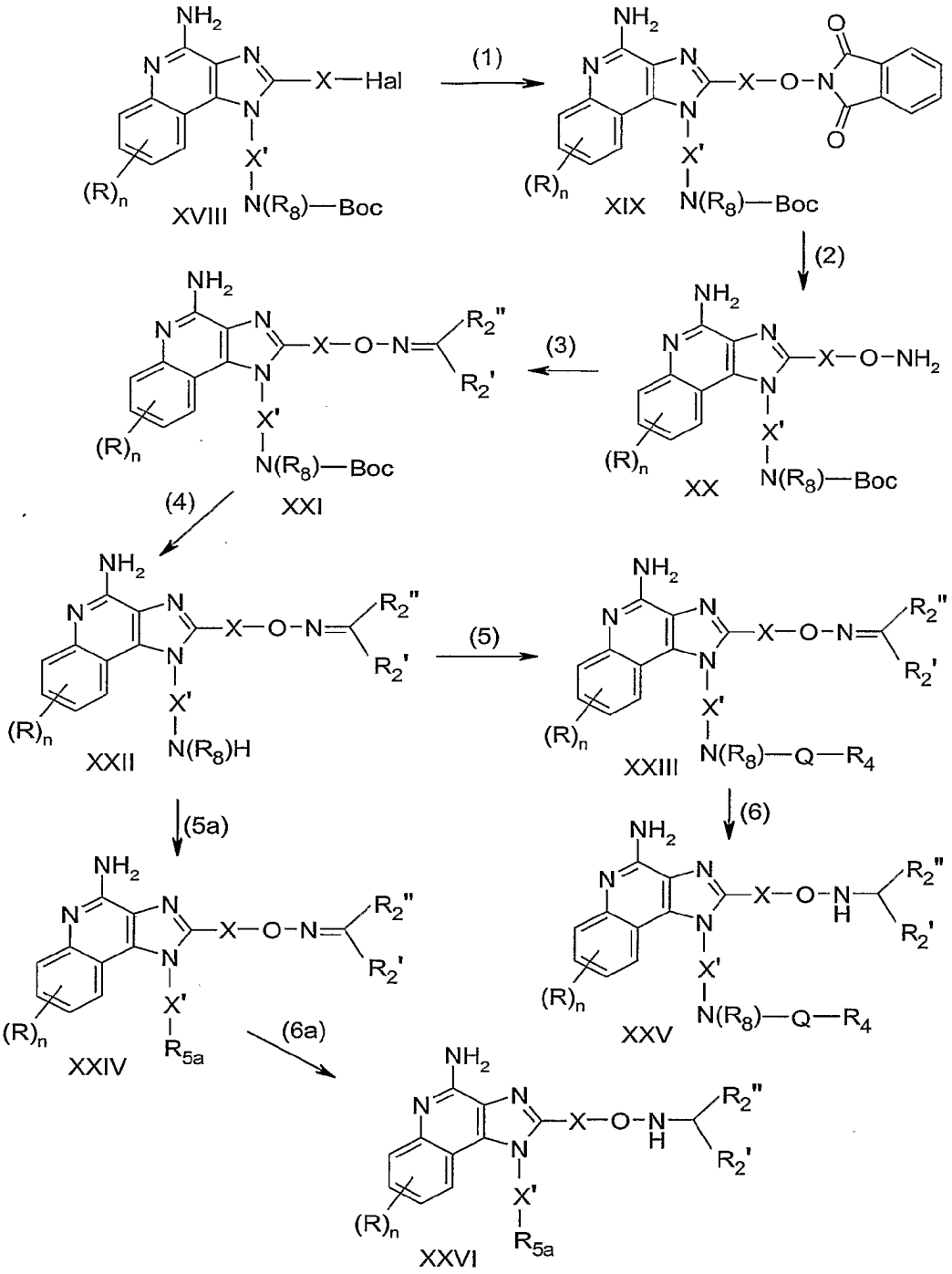
The reaction is preferably carried out by adding the chloroalkanoyl chloride compound to a compound of Formula XXII in a suitable solvent such as dichloromethane in the presence of a base such as *N*,*N*-diisopropylethylamine. The intermediate chloroalkanamide may optionally be isolated before treatment with a stronger base such as DBU at ambient temperature. If the intermediate chloroalkanamide is isolated, the reaction with DBU can be carried out in a suitable solvent such as DMF. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Ureas and thioureas of Formula XXIII (Q is, for example, $-C(O)\text{-}N(R_8)\text{-}$ or $-C(S)\text{-}N(R_8)\text{-}$) and XXIV can be prepared from 1*H*-imidazo[4,5-*c*]quinolin-2-yl oximes of Formula XXII using conventional methods. For example, a compound of Formula XXII can be reacted with an isocyanate of formula $R_4N{=}C{=}O$. The reaction can be carried out by adding the isocyanate to a solution of a compound of Formula XXII in a suitable solvent such as chloroform, optionally in the presence of a base such as *N*,*N*-diisopropylethylamine, or triethylamine, at ambient temperature. Alternatively, a compound of Formula XXII can be reacted with, for example, a thioisocyanate of formula

$R_4N=C=S$, a sulfonyl isocyanate of formula $R_4S(O)_2N=C=O$ or a carbamoyl chloride of formula $R_4N(R_8)C(O)Cl$. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In steps (6) and (6a) of Reaction Scheme II a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XXIII or Formula XXIV is reduced to provide a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XXV or Formula XXVI, each of which is a subgenus of Formulas I, II, III, and IIIa. The reduction is conveniently carried out by treating a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XXIII or Formula XXIV with excess sodium cyanoborohydride in a suitable solvent or solvent mixture such as methanol/acetic acid. The reaction can be carried out at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme II



Compounds of the invention can be prepared according to Reaction Scheme III where n is as defined above; each R_B is independently selected from the group consisting of hydroxy, alkyl, alkoxy, $-N(R_9)_2$; X_c is C_{1-10} alkylene; P is a removable protecting group,

such as an alkanoyloxy group (e.g., acetoxy) or an aroyloxy group (e.g., benzoyloxy); R_2' and R_2" are the same as R_1' and R_1" as defined above; and R_{1c} is a subset of R_1 as defined above, which does not include those groups that one skilled in the art would recognize as being susceptible to reduction in step (5). These groups include, for example, alkenyl, alkynyl, and aryl groups, and groups bearing nitro and –S- substitutents. In step (1) of Reaction Scheme III a quinoline-3,4-diamine of Formula Xa is reacted with a carboxylic acid of the formula, HO-X-CO_2H, with a trialkyl orthoester of the formula HO-X-C(O-C_{1-4} alkyl)$_3$, or with a combination thereof (wherein "alkyl" is a straight or branched chain) to provide a 1*H*-imidazo[4,5-*c*]quinolin-2-yl alcohol of Formula XXVII. The reaction is run with sufficient heating to drive off any alcohol or water formed as a byproduct of the reaction. Optionally a catalyst such as pyridine hydrochloride can be included. Compounds of Formula Xa are a subset of compounds of Formula X, which are shown in Reaction Scheme I.

In step (2) of Reaction Scheme III the hydroxyl group of a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXVII is protected with a removable protecting group such as an alkanoyloxy group (e.g., acetoxy) or aroyloxy group (e.g., benzoyloxy) to provide a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXVIII. Suitable protecting groups and reactions for their placement and removal are well known to those skilled in the art. See, for example, U.S. Patent No. 4,689,338 (Gerster), Examples 115 and 120 and 5,389,640 (Gerster et al.), Examples 2 and 3.

For some embodiments, it is possible to combine steps (1) and (2) when an acid chloride of the Formula PO-X-CO_2Cl is used under the conditions of step (1). Some acid chlorides of this type, for example, acetoxyacetyl chloride, are commercially available.

In step (3) of Reaction Scheme III a 1*H*-imidazo[4,5-*c*]quinoline of Formula XXVIII is oxidized to provide an *N*-oxide of Formula XXIX using a conventional oxidizing agent that is capable of forming *N*-oxides. The reaction can be carried out by treating a solution of a compound of Formula XXVIII in a suitable solvent such as chloroform or dichloromethane with 3-chloroperoxybenzoic acid at ambient temperature.

In step (4) of Reaction Scheme III an *N*-oxide of Formula XXIX is aminated and the protecting group removed to provide a 1*H*-imidazo[4,5-*c*]quinoline-4-amine of Formula XXX. The amination reaction is carried out in two parts. In part (i) a compound

of Formula XXIX is reacted with an acylating agent. Suitable acylating agents include alkyl- or arylsulfonyl chorides (e.g., benzenesulfonyl choride, methanesulfonyl choride, or *p*-toluenesulfonyl chloride). In part (ii) the product of part (i) is reacted with an excess of an aminating agent. Suitable aminating agents include ammonia (e.g. in the form of ammonium hydroxide) and ammonium salts (e.g., ammonium carbonate, ammonium bicarbonate, ammonium phosphate). The reaction can be carried out by dissolving a compound of Formula XXIX in a suitable solvent such as dichloromethane or chloroform, adding ammonium hydroxide to the solution, and then adding *p*-toluenesulfonyl chloride. The protecting group is removed using well-known methods. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (5) of Reaction Scheme III a 1*H*-imidazo[4,5-*c*]quinoline-4-amine of Formula XXX is reduced to provide a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-4-amine of Formula XXXI. The reaction can be conveniently carried out by suspending or dissolving a compound of Formula XXX in ethanol, adding a catalytic amount of rhodium on carbon, and hydrogenating. Alternatively, the reaction can be carried out by suspending or dissolving a compound of Formula XXX in trifluoroacetic acid, and adding platinum(IV) oxide, and hydrogenating. The reaction can be carried out in a Parr apparatus. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (6) of Reaction Scheme III a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-4-amine of Formula XXXI is treated with *N*-hydroxyphthalimide under Mitsunobu reaction conditions to provide an *N*-phthalimide-protected 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XXXII. The reaction is conveniently carried out by adding triphenylphosphine and *N*-hydroxyphthalimide to a solution of a compound of Formula XXXI in a suitable solvent such as tetrahydrofuran, and then slowly adding diethyl azodicarboxylate or diisopropyl azodicarboxylate. The reaction can be carried out at ambient temperature or at an elevated temperature, such as 60 °C. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Alternatively, step (6) may be carried out in two parts by (i) converting the hydroxy group in a compound of Formula XXXI to a leaving group and (ii) displacing the leaving

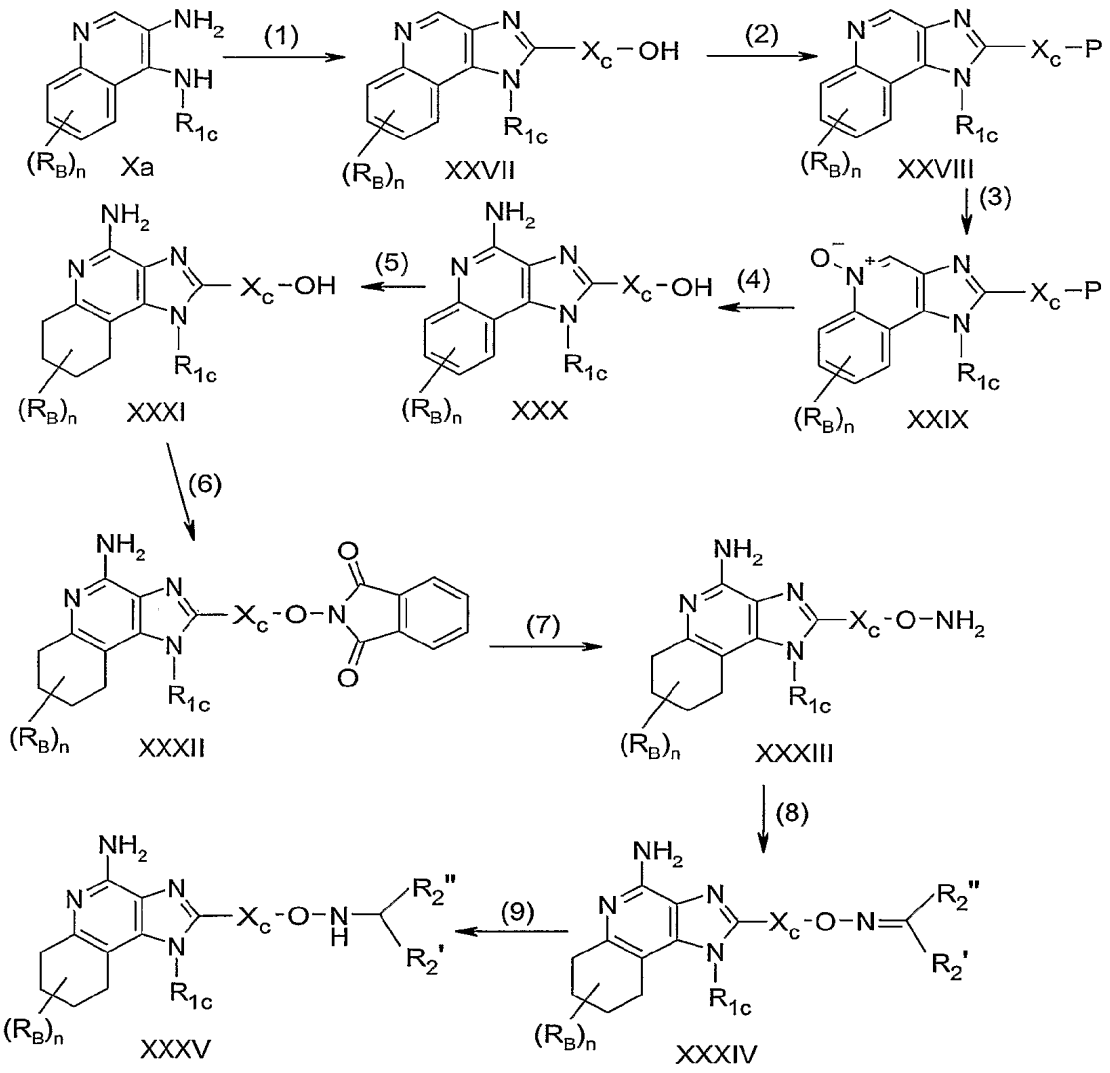
group with *N*-hydroxyphthalimide in the presence of a base. Part (i) of step (6) is conveniently carried out by treating the hydroxy-substituted 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinoline-4-amine of Formula XXXI with thionyl chloride in a suitable solvent such as 1,2-dichloroethane. The reaction may be carried out at ambient temperature, and the product can be isolated by conventional methods. Part (ii) of step (6) may be carried out under the conditions described in step (4) of Reaction Scheme I, and the product of Formula XXXII or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (7) of Reaction Scheme III an *N*-phthalimide-protected 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XXXII is converted to a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XXXIII. Removal of the *N*-phthalimide protecting group is conveniently carried out by adding hydrazine to a suspension of an *N*-phthalimide-protected 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XXXII in a suitable solvent such as ethanol. The reaction can be carried out at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (8) of Reaction Scheme III a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XXXIII is reacted with an aldehyde or ketone of formula $R_2'C(O)R_2''$ to provide a 6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XXXIV as in step (3) of Reaction Scheme II. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (9) of Reaction Scheme III a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XXXIV is reduced to provide a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XXXV, which is a subgenus of Formulas I, II, IV and IVa. The reduction is carried out as described in step (7) of Reaction Scheme I. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme III

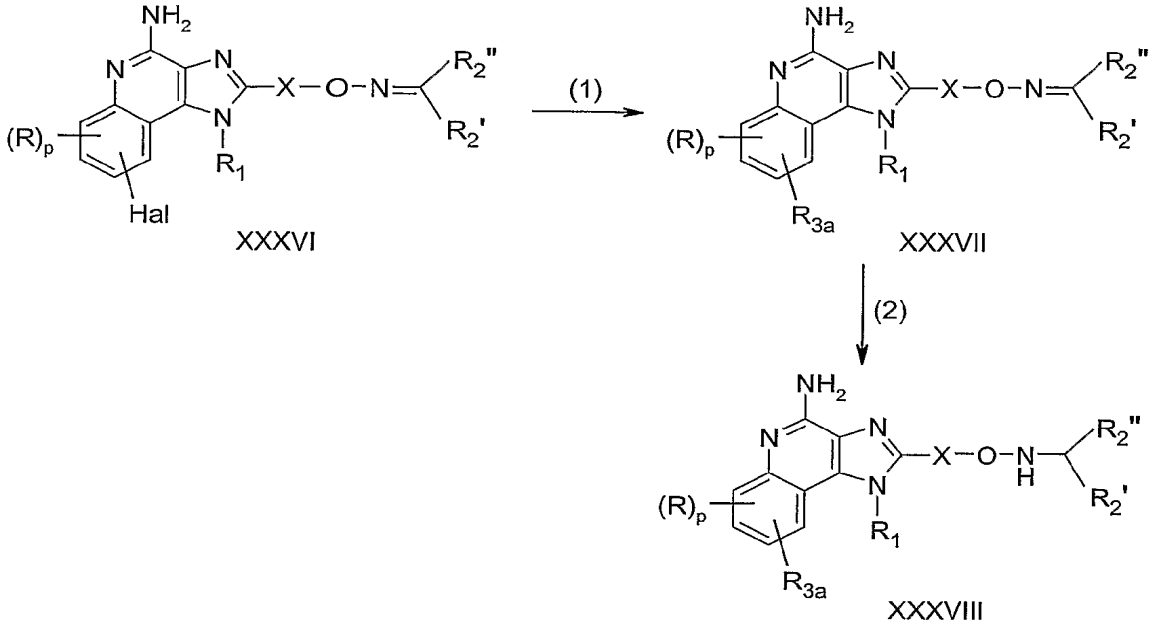


Compounds of the invention can be prepared according to Reaction Scheme IV where R_1, R, X, and Hal are as defined above, p is 0 to 3, R_2' and R_2'' are the same as R_1' and R_1'' as defined above, and R_{3a} is $-R_{4b}$, $-X'_a-R_4$, $-X'_b-Y-R_4$, or $-X'_b-R_5$; where X'_a is alkenylene; X'_b is arylene, heteroarylene, and alkenylene interrupted or terminated by arylene or heteroarylene; R_{4b} is aryl or heteroaryl where the aryl or heteroaryl groups can be unsubstituted or substituted as defined in R_4 above; and R_4, R_5, and Y are as defined above. In step (1) of Reaction Scheme IV a halogen substituted 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XXXVI is coupled with a boronic acid of the formula R_{3a}-$B(OH)_2$ (or the corresponding anhydride or esters, R_{3a}-B(O-alkyl)$_2$, thereof) using

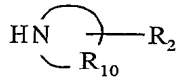
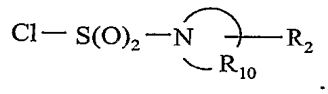
Suzuki coupling conditions to provide a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XXXVII. A compound of Formula XXXVI is combined with a boronic acid of the formula R_{3a}-$B(OH)_2$ in the presence of palladium (II) acetate, triphenylphosphine and a base such as aqueous sodium carbonate in a suitable solvent such as *n*-propanol or *n*-propanol and water. The reaction can be carried out at an elevated temperature (e.g., 80 °C-100 °C). The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods. Halogen substituted 1*H*-imidazo[4,5-*c*]quinolin-2-yl oximes of Formula XXXVI can be prepared as described above in steps (1)-(6) of Reaction Scheme I or steps (1) – (5) or (5a) or Reaction Scheme II, wherein one of the R groups is Hal. Numerous boronic acids of Formula R_{3a}-$B(OH)_2$, anhydrides thereof, and boronic acid esters of Formula R_{3a}-$B(O\text{-alkyl})_2$ are commercially available; others can be readily prepared using known synthetic methods.

In step (2) of Reaction Scheme IV a 1*H*-imidazo[4,5-*c*]quinolin-2-yl oxime of Formula XXXVII is reduced to provide a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XXXVIII, which is a subgenus of Formulas I, II, III, and IIIa. The reduction is carried out as described in step (7) of Reaction Scheme I. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

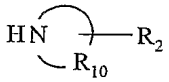
Reaction Scheme IV



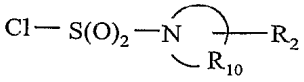
Compounds of the invention can be prepared according to Reaction Scheme V where R, R_1, R_2, X, and n are as defined above, and Y_a' is Y' defined above, excluding a bond. In step (1) of Reaction Scheme V, a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XV is converted to a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XXXIX, a subgenus of Formulas I, II, III, and IIIa, using conventional methods. For example, sulfonamides of Formula XXXIX (Y_a' is $-S(O)_2-$) can be prepared by reacting a compound of Formula XV with a sulfonyl chloride of formula $R_2S(O)_2Cl$. The reaction can be carried out at ambient temperature in an inert solvent such as chloroform or dichloromethane by adding the sulfonyl chloride to a compound of Formula XV in the presence of a base such as *N*,*N*-diisopropylethylamine, triethylamine, or pyridine.

Sulfamides of Formula XXXIX (Y_a' is $-S(O)_2-N(R_8)-$ or ) can be prepared by reacting a compound of Formula XV with sulfuryl chloride to generate a sulfamoyl chloride in situ, and then reacting the sulfamoyl chloride with an amine of formula $HN(R_8)R_2$, or  , or by reacting a compound of Formula XV with a sulfamoyl chloride of formula $R_2(R_8)NS(O)_2Cl$ or  . The product or

a pharmaceutically acceptable salt thereof can be isolated using conventional methods. Many sulfonyl chlorides of formula $R_2S(O)_2Cl$, amines of formulas $HN(R_8)R_2$, and



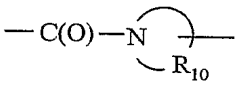
, and some sulfamoyl chlorides of formulas $R_2(R_8)NS(O)_2Cl$ and



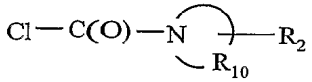
are commercially available; others can be prepared using known synthetic methods.

Amides of Formula XXXIX (Y_a' is –C(O)-) can be prepared from 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamines of Formula XV using conventional methods. For example, a compound of Formula XV can be reacted with an acid chloride of formula $R_2C(O)Cl$ to provide a compound of Formula XXXIX. The reaction can be carried out by adding the acid chloride to a solution of a compound of Formula XV in a suitable solvent such as chloroform, optionally in the presence of a base such as *N*,*N*-diisopropylethylamine, triethylamine, or pyridine, at ambient temperature. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Ureas and thioureas of Formula XXXIX (Y_a' is -C(O)-N(R_8)-, -C(S)-N(R_8)-, -C(O)-N(R_8)-S(O)$_2$-, -C(O)-N(R_8)-C(O)-, -C(S)-N(R_8)-C(O)-, or

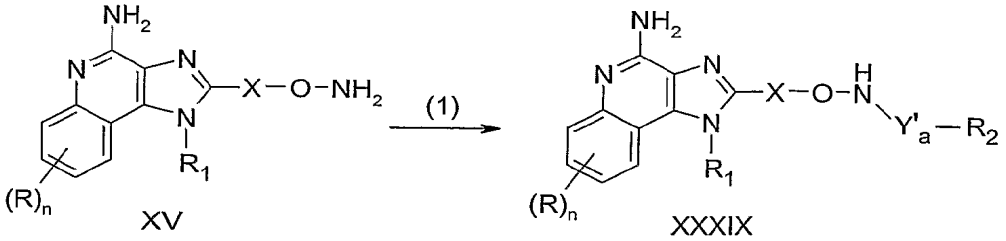


) can be prepared from 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamines of Formula XV using conventional methods. For example, a compound of Formula XV can be reacted with an isocyanate of formula $R_2N=C=O$. The reaction can be carried out by adding the isocyanate to a solution of a compound of Formula XV in a suitable solvent such as chloroform, optionally in the presence of a base such as *N*,*N*-diisopropylethylamine, or triethylamine, at ambient temperature. Alternatively, a compound of Formula XV can be reacted with a thioisocyanate of formula $R_2N=C=S$, a sulfonyl isocyanate of formula $R_2S(O)_2N=C=O$ or a carbamoyl chloride of formula $R_2N(R_8)C(O)Cl$ or



. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme V

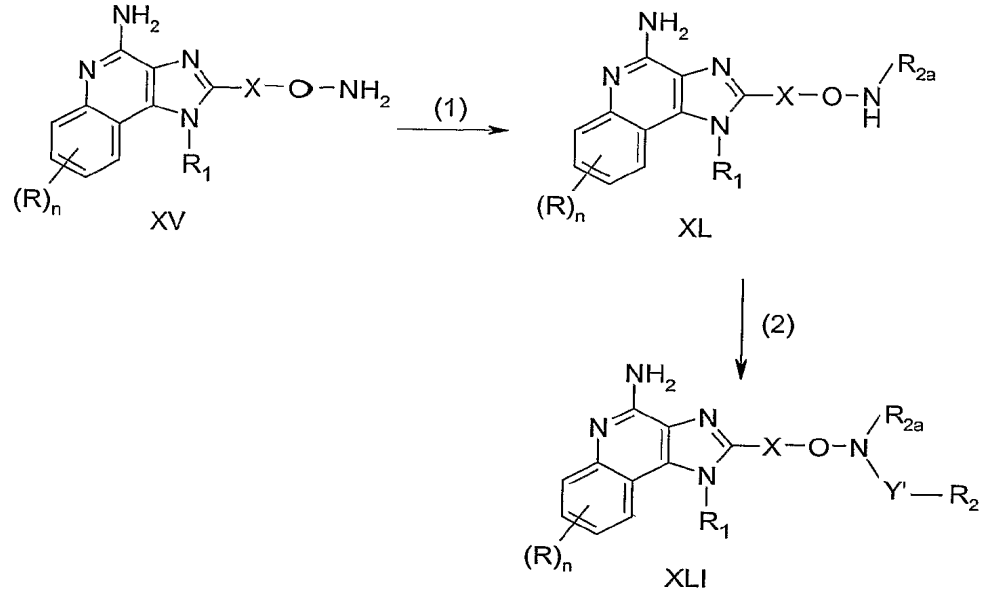


Compounds of the invention wherein R_{2a} is other than hydrogen can be prepared according to Reaction Scheme VI where R, R_1, R_2, X, Y', and n are as defined above.

In step (1) of Reaction Scheme VI, a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XL, a subgenus of Formulas I, II, III, and IIIa, is prepared by reductive alkylation of a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XV. The reaction is carried out in two steps, (i) reacting a compound of Formula XV with the appropriate aldehyde to provide an oxime and (ii) reducing the oxime, using the methods of steps (6) and (7), respectively, of Reaction Scheme I.

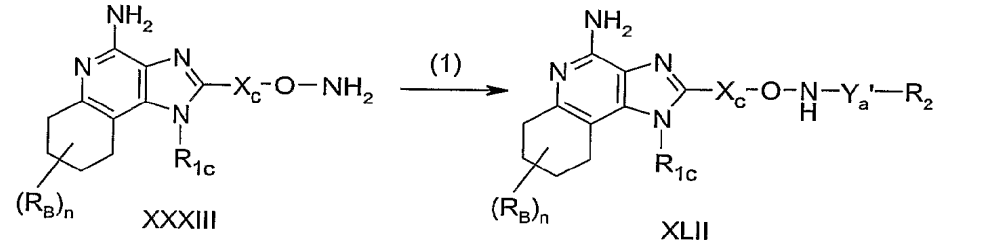
In step (2) of Reaction Scheme VI, a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XL is converted to a 1*H*-imidazo[4,5-*c*]quinolin-2-yl hydroxylamine of Formula XLI, a subgenus of Formulas I, II, and III. Compounds of Formula XLI wherein Y' is a bond are prepared by subjecting the compound of Formula XL to a second alkylation. Compounds of Formula XLI wherein Y' is other than a bond are prepared using the methods of Reaction Scheme V. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme VI



For some embodiments, tetrahydroquinolines of the invention can be prepared according to Reaction Scheme VII, wherein R_B, R_{1c}, X_c, Y_a', R_2, and n are as defined above. The reaction in Reaction Scheme VII can be carried out according to one of the methods described in Reaction Scheme V to provide a tetrahydroquinoline of Formula XLII, a subgenus of Formulas I, II, IV, and IVa. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods. Tetrahydroquinolines of Formula XXXIII can also be treated according to the methods described in Reaction Scheme V to provide compounds of the invention.

Reaction Scheme VII



Compounds of the invention can be prepared according to Reaction Scheme VIII where R, R_1, R_2, R_2', R_2", R_{2a}, X, Y', and Hal are as defined above; E is carbon

(imidazoquinoline ring) or nitrogen (imidazonaphthyridine ring); n is an integer from 0 to 4 (imidazoquinoline ring) or 0 to 3 (imidazonaphthyridine ring) with the proviso that when m is 1, then n is 0 or 1; and D is –Br, –I, or –OCH_2Ph; wherein Ph is phenyl. In step (1) of Reaction Scheme VIII, an aniline or aminopyridine of Formula XLIII is treated with the condensation product generated from 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) and triethyl orthoformate to provide an imine of Formula XLIV. The reaction is conveniently carried out by adding a solution of an aniline or aminopyridine of Formula XLIII to a heated mixture of Meldrum's acid and triethyl orthoformate and heating the reaction at an elevated temperature. The product can be isolated using conventional methods. Many anilines and aminopyridines of Formula XLIII are commercially available; others can be prepared by known synthetic methods. For example, benzyloxypyridines of Formula XLIII can be prepared using the method of Holladay et al., *Biorg. Med. Chem. Lett.*, *8*, pp. 2797-2802, (1998).

In step (2) of Reaction Scheme VIII, an imine of Formula XLIV undergoes thermolysis and cyclization to provide a compound of Formula XLV. The reaction is conveniently carried out in a medium such as DOWTHERM A heat transfer fluid at a temperature of 200 °C to 250 °C. The product can be isolated using conventional methods. Isomers of the compound of Formula XLIII or Formula XLV, wherein E is nitrogen, can also be synthesized and can be used to prepare compounds of the invention.

In step (3) of Reaction Scheme VIII, a compound of Formula XLV is nitrated under conventional nitration conditions to provide a compound of Formula XLVI. The reaction is conveniently carried out by adding nitric acid to the compound of Formula XLV in a suitable solvent such as propionic acid and heating the mixture at an elevated temperature. The product can be isolated using conventional methods.

In step (4) of Reaction Scheme VIII, a 3-nitro[1,5]naphthyridin-4-ol or 3-nitroquinolin-4-ol of Formula XLVI is chlorinated using conventional chlorination chemistry to provide a 4-chloro-3-nitro[1,5]naphthyridine or 4-chloro-3-nitroquinoline of Formula XLVII. The reaction is conveniently carried out by treating the compound of Formula XLVI with phosphorous oxychloride in a suitable solvent such as DMF. The reaction can be carried out at ambient temperature or at an elevated temperature such as 100 °C, and the product can be isolated using conventional methods.

The 4-chloro-3-nitro[1,5]naphthyridine of Formula XLVII wherein m and n are both 0 is known and can be readily prepared using a known synthetic route; see for example, U.S. Patent No. 6,194,425 (Gerster et al.).

In step (5) of Reaction Scheme VIII, a 4-chloro-3-nitro[1,5]naphthyridine or 4-chloro-3-nitroquinoline of Formula XLVII is treated with an amine of Formula R_1-NH_2 to provide a compound of Formula XLVIII. Several amines of Formula R_1-NH_2 are commercially available; others can be prepared by known synthetic methods. The reaction is conveniently carried out by adding the amine of Formula R_1-NH_2 to a solution of the 4-chloro-3-nitro[1,5]naphthyridine or 4-chloro-3-nitroquinoline of Formula XLVII in a suitable solvent such as dichloromethane in the presence of a tertiary amine such as triethylamine. The reaction can be carried out at ambient temperature or at a sub-ambient temperature such as, for example, 0 °C. The reaction product can be isolated using conventional methods.

In step (6) of Reaction Scheme VIII, a compound of Formula XLVIII is reduced to provide a diamine of Formula XLIX. The reaction can be carried out by hydrogenation using a heterogeneous hydrogenation catalyst such as palladium on carbon or platinum on carbon. The hydrogenation is conveniently carried out in a Parr apparatus in a suitable solvent such as toluene, methanol, acetonitrile, or ethyl acetate. For compounds of the Formula XLVIII wherein m is 1 and D is -OCH_2Ph, the preferred catalyst is platinum on carbon. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

Alternatively, the reduction in step (6) can be carried out using nickel boride, prepared *in situ* from sodium borohydride and nickel(II) chloride. The reduction is conveniently carried out by adding a solution of a compound of Formula XLVIII in a suitable solvent or solvent mixture such as dichloromethane/methanol to a mixture of excess sodium borohydride and catalytic nickel(II) chloride in methanol. The reaction can be carried out at ambient temperature. The product can be isolated using conventional methods.

In step (7) of Reaction Scheme VIII, a diamine of Formula XLIX, is reacted with a carboxylic acid equivalent to provide a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine or 1*H*-imidazo[4,5-*c*]quinoline of Formula L. The carboxylic acid or equivalent is selected such

that it will provide the desired –X-Hal substituent in a compound of Formula L and the reaction can be carried out as described in step (1) of Reaction Scheme I. When an acid chloride, for example chloroacetyl chloride, is used as the carboxylic acid equivalent, the reaction can be carried out in two steps. Part (i) of step (7) is conveniently carried out by adding the acid chloride to a solution of a diamine of Formula XLIX in a suitable solvent such as dichloromethane, chloroform, or acetonitrile. Optionally, a tertiary amine such as triethylamine, pyridine, or 4-dimethylaminopyridine can be added. The reaction can be carried out at ambient temperature. The amide product or the salt thereof can be isolated and optionally purified using conventional techniques. Part (ii) of step (7) involves heating the amide prepared in part (i) in the presence of base to provide a 1*H*-imidazo[4,5-*c*][1,5]naphthyridine or 1*H*-imidazo[4,5-*c*]quinoline of Formula L. The reaction is conveniently carried out in a suitable solvent such as ethanol in the presence of a base such aqueous sodium hydroxide, aqueous potassium carbonate, or triethylamine at elevated temperature. In some instances, the product of Formula L may be obtained directly from Part (i). Alternatively, a diamine of Formula XLIX can be treated with ethyl chloroacetimidate hydrochloride as the carboxylic acid equivalent to provide a compound wherein X is methylene. The reaction is carried out in a suitable solvent such as chloroform at ambient temperature and the product of Formula L can be isolated using conventional methods. Ethyl chloroacetimidate hydrochloride is a known compound that can be prepared according to the literature procedure: Stillings, M. R. et al., *J. Med. Chem.*, 29, pp. 2280-2284 (1986).

In steps (8) – (10) of Reaction Scheme VIII, a halogen-substituted 1*H*-imidazo[4,5-*c*][1,5]naphthyridine or 1*H*-imidazo[4,5-*c*]quinoline of Formula L can be converted into phthalimide-substituted 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine or 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula LIII using the chemistry described in steps (2) – (4) of Reaction Scheme I. Steps (8) and (9) can alternatively be combined and carried out as a one-pot procedure by adding 3-chloroperoxybenzoic acid to a solution of a compound of Formula L in a solvent such as dichloromethane or chloroform and then adding ammonium hydroxide and *p*-toluenesulfonyl chloride without isolating the *N*-oxide of Formula LI. Compounds of Formula LI, LII, and LIII or their pharmaceutically acceptable salts can be isolated using conventional methods.

In steps (11) and (12) of Reaction Scheme V, a phthalimide-substituted 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine or 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula LIII is converted to a hydroxylamine-subsitituted 1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine or 1*H*-imidazo[4,5-*c*]quinolin-4-amine of Formula LIV which is condensed with an aldehyde or ketone to form an oxime of Formula LV, sequentially using the chemistry described in steps (5) and (6) of Reaction Scheme I. Compounds of Formula LIV and LV or their pharmaceutically acceptable salts can be isolated using conventional methods.

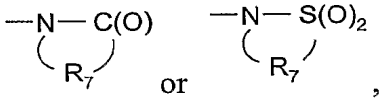
In step (13) of Reaction Scheme VIII, an oxime of Formula LV is reduced to provide a hydroxylamine of Formula LVI, a subgenus of Formulas I and II. The reduction is conveniently carried out by treating the oxime of Formula LV with excess sodium cyanoborohydride in a suitable solvent or solvent mixture such as methanol/acetic acid. Optionally, hydrochloric acid may be added. The reaction can be carried out at ambient temperature or at elevated temperature. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (14) of Reaction Scheme VIII, a hydroxylamine of Formula LVI is converted to a compound of Formula LVII, a subgenus of Formulas I and II. The reaction is carried out using one of the methods described in Reaction Scheme V or step (2) of Reaction Scheme VI. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Alternatively, a compound of Formula LIV can be converted to a compound of Formula LVIII, a subgenus of Formulas I and II, as shown in step (12a) of Reaction Scheme VIII. The transformation is conveniently carried out by using the conditions described in Reaction Scheme V and step (2) of Reaction Scheme VI. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (13a) of Reaction Scheme VIII, a compound of Formula LVIII is alkylated to provide a compound of Formula LVII. The reaction can be carried out with an alkylating agent that is generated in situ from an alcohol of Formula R_{2a}-OH under Mitsunobu reaction conditions (described in step (6) of Reaction Scheme III) or an alkylating agent of Formula R_{2a}-Br or R_{2a}-I in the presence of a base such as cesium carbonate in a suitable solvent such as DMF. The latter reaction may be carried out at

ambient temperature for reactive alkylating agents such as, for example, methyl iodide, benzyl bromide, and substituted benzyl bromides, or at an elevated temperature. Optionally, catalytic tetrabutylammonium hydrogensulfate can be added. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods. One skilled in the art would recognize that the reactions described for the alkylation step would probably not be successful for R_{2a} groups that are difficult to introduce via bimolecular nucleophilic substitution reactions. These groups include, for example, sterically hindered alkyl groups.

A compound of Formula LVIII in which R_{2a} and R_2 together with the nitrogen atom and Y' group to which they are bonded join together to form a ring of Formula  or , can be prepared in a two-step procedure from a compound of Formula LIV using the methods described in step 5a of Reaction Scheme II. Alternatively, a reagent of the Formula P-O-R_7C(O)Cl, wherein P is a protecting group, may react with a compound of Formula LIV to generate an isolable intermediate that can then be deprotected to yield a hydroxyalkanamide. The isolable hydroxyalkanamide is cyclized under Mitsunobu conditions, described in step (6) of Reaction Scheme III. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

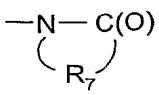
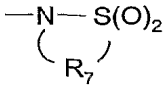
For some embodiments, compounds shown in Reaction Scheme VIII can be further elaborated using conventional synthetic methods. For example, an amine of Formula R_1-NH_2, used in step (5) of Reaction Scheme VIII, may contain a protected functional group, such as a *tert*-butoxycarbonyl-protected amino group. The protecting group may be removed after step (14) of Reaction Scheme V to reveal an amine on the R_1 group. An amino group introduced in this manner may be further functionalized using the chemistry described in steps (5) and (5a) of Reaction Scheme II to provide compounds of the Formula LVII in which R_1 is -X'-N(R_8)-Q-R_4 or -X'-R_{5a}. Alternatively, the protecting group may be removed after step (7) in Reaction Scheme VIII and the resulting amino group may be functionalized as described above before step (8). The resulting compound of Formula L can be subjected to steps (8) - (14) of Reaction Scheme VIII to provide a compound of Formula LVII wherein R_1 is –X'-N(R_8)-Q-R_4 or -X'-R_{5a}.

Alternatively, the amine of Formula R_1-NH_2 used in step (5) of Reaction Scheme VIII may contain an appropriately-protected hydroxyl group, for example, a *tert*-butyldimethylsilyl-protected hydroxyl group. The protecting group may be removed after step (14) in Reaction Scheme VIII to provide an alcohol on the R_1 group. An alcohol introduced in this manner into a compound of Formula LVII may be converted into a hydroxylamine upon treatment with *N*-hydroxyphthalimide using the Mitsunobu reaction conditions described in step (6) of Reaction Scheme III, followed by deprotection of the resulting phthalimide-protected hydroxylamine with hydrazine in ethanol. A hydroxylamine on the R_1 group can undergo reaction with a ketone or aldehyde of Formula R_1'C(O)R_1" to form an oxime using the reaction conditions described in step (6) of Reaction Scheme I to yield a compound of Formula LVII in which R_1 is -X"-O-N=C(R_1')(R_1") where X", R_1', and R_1" are as defined above.

A hydroxylamine on the R_1 group of a compound of Formula LVII, prepared as described above, can also be further functionalized to a compound of the Formula LVII in which R_1 is -X"-O-NR_{1a}-Y'-R_{1b} wherein Y' is -C(O)-, -$S(O)_2$-, -C(O)-N(R_8)-, -C(S)-N(R_8)-, -C(O)-N(R_8)-$S(O)_2$-, -C(O)-N(R_8)-C(O)-, –$S(O)_2$-N(R_8)-; R_{1a} is hydrogen, and R_{1b} is as defined above using, respectively, an acid chloride, a sulfonyl chloride or a sulfonic anhydride; an isocyanate; an acyl isocyanate, an isothiocyanate, a sulfonyl isocyanate, a carbamoyl chloride, or a sulfamoyl chloride. The reaction can be carried out using the conditions described in step (5) of Reaction Scheme II. A large number of the reagents listed above are commercially available; others can be readily prepared using known synthetic methods.

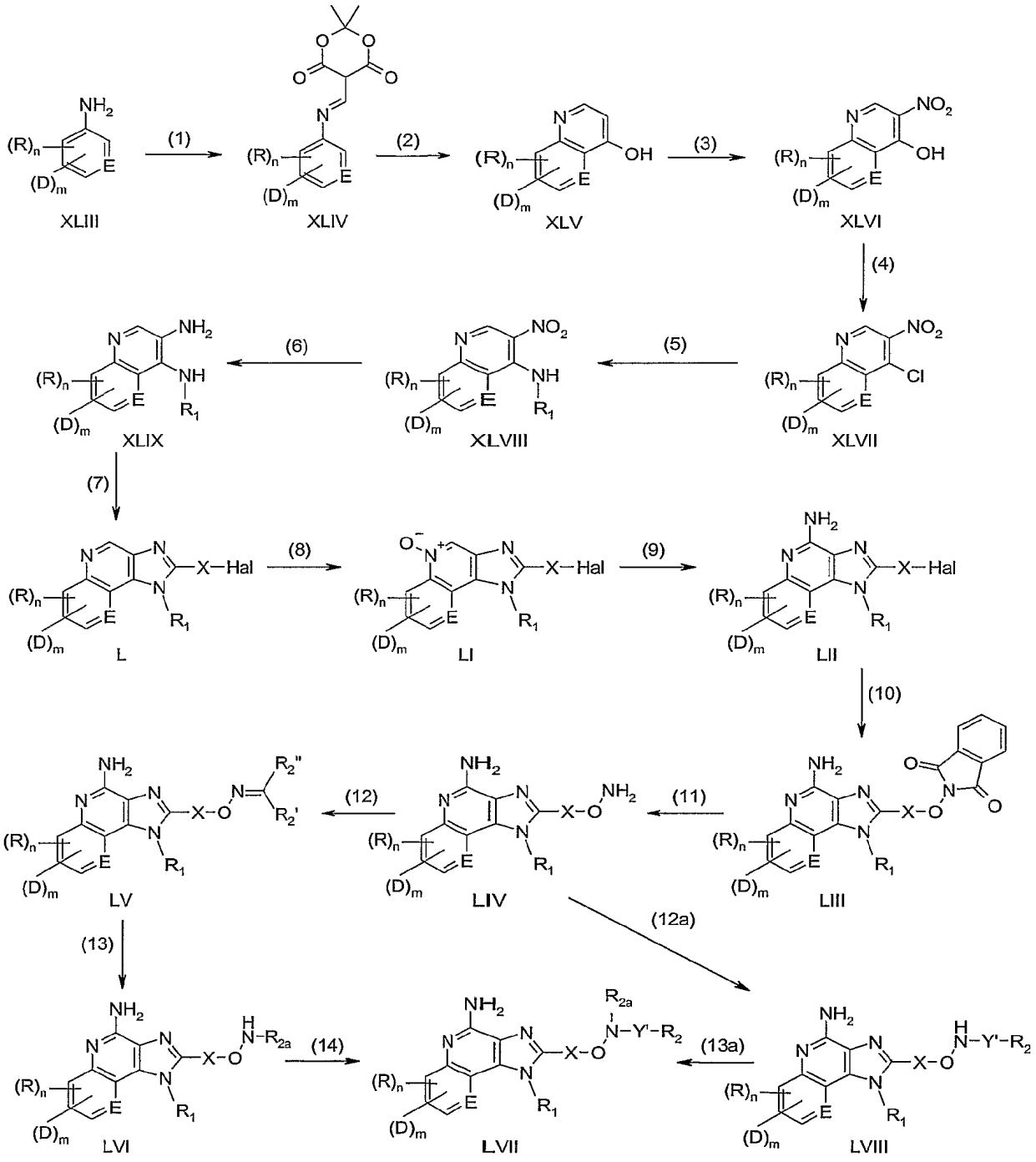
A compound of Formula LVII in which R_1 is -X"-O-NR_{1a}-Y'-R_{1b} wherein Y' is a bond, –C(O)-, -C(S)-, -$S(O)_2$-, or -C(O)-C(O)-; R_{1b} is defined above, and R_{1a} is hydrogen, can be derivatized further upon treatment with an alkylating agent that is generated in situ from an alcohol of Formula R_{1a}-OH under Mitsunobu reaction conditions or an alkylating agent of Formula R_{1a}-Br or R_{1a}-I as described in step (13a) above.

A compound of Formula LVII in which R_1 is -X"-O-NR_{1a}-Y'-R_{1b}, where R_{1a} and R_{1b} together with the nitrogen atom and Y' group to which they are bonded join together to form a ring of Formula

, can be prepared in a two-step procedure from a compound of Formula LVII in which R_1 is -X"-O-NH_2, using one of the methods described in step 5a of Reaction Scheme II or step 13a above.

Reaction Scheme VIII



Compounds of the invention can be prepared according to Reaction Scheme IX, wherein D, E, R, R_1, R_2, R_{2a}, X, and Y'are as defined above, m is 1, n is 0 or 1, and R_{3b}

and R_{3c} are as defined below. In Reaction Scheme IX, when D is -Br or -I, step (1) is used to react a 1*H*-imidazo[4,5-*c*]quinoline-4-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine-4-amine of Formula LVII using known palladium-catalyzed coupling reactions such as the Suzuki coupling and the Heck reaction. For example, a bromo or iodo-substituted compound of Formula LVII undergoes Suzuki coupling with a boronic acid of Formula R_{3a}-$B(OH)_2$, an anhydride thereof, or a boronic acid ester of Formula R_{3a}-$B(O\text{-alkyl})_2$, wherein R_{3a} is as defined above, according to the method described in Reaction Scheme IV. The product of Formula LIX, a subgenus of Formulas I and II wherein R_{3b} is the same as R_{3a}, or a pharmaceutically acceptable salt thereof, can be isolated by conventional methods.

The Heck reaction can also be used in step (1) of Reaction Scheme IX to provide compounds of Formula LIX, wherein R_{3b} is $-X'_a$-R_{4b} and $-X'_a$-Y-R_4, wherein X'_a, Y, R_{4b}, and R_4 are as defined above. The Heck reaction is carried out by coupling a compound of Formula LVII with a compound of the Formula $H_2C{=}C(H)$-R_{4b} or $H_2C{=}C(H)$-Y-R_4. Several of these vinyl-substituted compounds are commercially available; others can be prepared by known methods. The reaction is conveniently carried out by combining the compound of Formula LVII and the vinyl-substituted compound in the presence of palladium (II) acetate, triphenylphosphine or tri-*ortho*-tolylphosphine, and a base such as triethylamine in a suitable solvent such as acetonitrile or toluene. The reaction can be carried out at an elevated temperature such as 100 °C -120 °C under an inert atmosphere. The product of Formula LIX or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Compounds of Formula LIX, wherein R_{3b} is $-X'_c$-R_4, X'_c is alkynylene, and R_4 is as defined above, can also be prepared by palladium catalyzed coupling reactions such as the Stille coupling or Sonogashira coupling. These reactions are carried out by coupling a compound of Formula LVII with a compound of the Formula $(alkyl)_3Sn$-$C{\equiv}C$-R_4, $(alkyl)_3Si$-$C{\equiv}C$-R_4, or H-$C{\equiv}C$-R_4.

Compounds of Formula LIX prepared as described above by palladium-mediated coupling reactions, wherein R_{3b} is $-X'_a$-R_4, -X'_a-Y-R_4, -X'_{b2}-Y-R_4, -X'_{b2}-R_5, or $-X'_c$-R_4, where X'_{b2} is alkenylene interrupted or terminated by arylene or heteroarylene, and X'_a,

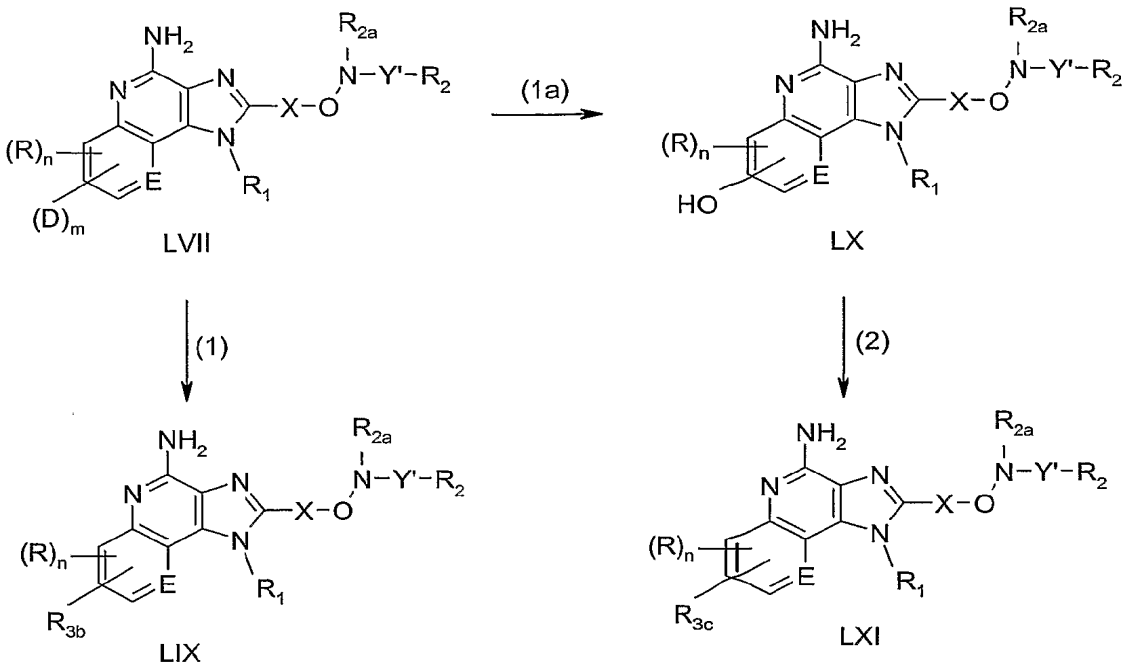
X'_c, Y, R_4, and R_5 are as defined above, can undergo reduction of the alkenylene or alkynylene group present to provide compounds of Formula LIX wherein R_{3b} is $-X'_d$-R_4, -X'_d-Y-R_4, -X'_e-Y-R_4, or $-X'_e$-R_5, where X'_d is alkylene; X'_e is alkylene interrupted or terminated by arylene or heteroarylene; and R_4, R_5, and Y are as defined above. The reduction can be carried out by hydrogenation using a conventional heterogeneous hydrogenation catalyst such as palladium on carbon. The reaction can conveniently be carried out on a Parr apparatus in a suitable solvent such as ethanol, methanol, or mixtures thereof. The product or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Compounds of Formula LVII wherein D is $-OCH_2Ph$ can be converted in Reaction Scheme IX to compounds of Formula LXI wherein R_{3c} is -O-R_{4b}, -O-X'-R_4, -O-X'-Y-R_4, or -O-X'-R_5; wherein R_4, R_{4b}, R_5, X', and Y are as defined above. In step (1a) of Reaction Scheme IX, the benzyl group in a 1*H*-imidazo[4,5-*c*]quinoline-4-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine-4-amine of Formula LVII, wherein D is $-OCH_2Ph$, is cleaved to provide a hydroxy group. The cleavage is conveniently carried out on a Parr apparatus under hydrogenolysis conditions using a suitable heterogeneous catalyst such as palladium or platinum on carbon in a solvent such as ethanol. Alternatively, the reaction can be carried out by transfer hydrogenation in the presence of a suitable hydrogenation catalyst. The transfer hydrogenation is conveniently carried out by adding ammonium formate to a solution of a compound of Formula LVII in a suitable solvent such as ethanol in the presence of a catalyst such as palladium on carbon. The reaction is carried out at an elevated temperature, for example, the refluxing temperature of the solvent. The product of Formula LX, a subgenus of Formulas I and II, or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (2) of Reaction Scheme IX, a hydroxy-substituted 1*H*-imidazo[4,5-*c*]quinoline-4-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine-4-amine of Formula LX is converted to a compound of Formula LXI, a subgenus of Formula I and II wherein R_{3c} is -O-R_{4b}, -O-X'-R_4, -O-X'-Y-R_4, or -O-X'-R_5, using a Williamson-type ether synthesis. The reaction is effected by treating a hydroxy-substituted 1*H*-imidazo[4,5-*c*]quinoline-4-amine or 1*H*-imidazo[4,5-*c*][1,5]naphthyridine-4-amine of Formula LX with an aryl, alkyl, or arylalkylenyl halide of Formula Halide-R_{4b}, Halide-alkylene-R_4, Halide-alkylene-Y-R_4, or

Halide-alkylene-R_5 in the presence of a base. Numerous alkyl, arylalkylenyl, and aryl halides of these formulas are commercially available, including substituted benzyl bromides and chlorides, substituted or unsubstituted alkyl or arylalkylenyl bromides and chlorides, and substituted fluorobenzenes. Other halides of these formulas can be prepared using conventional synthetic methods. The reaction is conveniently carried out by combining an alkyl, arylalkylenyl, or aryl halide with the hydroxy-substituted compound of Formula LX in a solvent such as DMF in the presence of a suitable base such as cesium carbonate. Optionally, catalytic tetrabutylammonium bromide can be added. The reaction can be carried out at ambient temperature or at an elevated temperature, for example 65 °C or 85 °C, depending on the reactivity of the halide reagent. Alternatively, step (2) may be carried out using the Ullmann ether synthesis, in which an alkali metal aryloxide prepared from the hydroxy-substituted compound of Formula LX reacts with an aryl halide in the presence of copper salts, to provide a compound of Formula LXI, where R_{3c} is -O-R_{4b}, -O-X'_f-R_4, or -O-X'_f-Y-R_4, wherein X'_f is an arylene or heteroarylene. Numerous substituted and unsubstituted aryl halides are commercially available; others can be prepared using conventional methods. The product of Formula LXI, prepared by either of these methods, or pharmaceutically acceptable salt thereof can be isolated using conventional methods.

Reaction Scheme IX



For some embodiments, compounds of the invention are prepared according to Reaction Scheme X, where R_1, R_2, R_2', R_2", R_{2a}, X, Y', R_{A2}, R_{B2}, and Hal are as defined above, and Ph is phenyl. In step (1) of Reaction Scheme X, a 2,4-dichloro-3-nitropyridine of Formula LXII is reacted with an amine of the Formula H_2N-R_1 to form a 2-chloro-3-nitropyridine of Formula LXIII. The reaction is conveniently carried out by combining an amine of Formula H_2N-R_1 and a 2,4-dichloro-3-nitropyridine of Formula LXII in the presence of a base such as triethylamine in an inert solvent such as DMF. The reaction can be carried out at ambient temperature, and the product can be isolated from the reaction mixture using conventional methods. Many amines of Formula H_2N-R_1 are commercially available; others can be prepared by known synthetic methods. Many 2,4-dichloro-3-nitropyridines of the Formula LXII are known and can be readily prepared using known synthetic methods (see, for example, Dellaria et al, U.S. Pat. No. 6,525,064 and the references cited therein).

In step (2) of Reaction Scheme X, a 2-chloro-3-nitropyridine of Formula LXIII is reacted with an alkali metal azide to provide an 8-nitrotetrazolo[1,5-*a*]pyridin-7-amine of Formula LXIV. The reaction can be carried out by combining the compound of Formula

LXIII with an alkali metal azide, for example, sodium azide, in a suitable solvent such as acetonitrile/water, preferably 90/10 acetonitrile/water, in the presence of cerium(III) chloride, preferably cerium(III) chloride heptahydrate. Optionally, the reaction can be carried out with heating, for example, at the reflux temperature. Alternatively, the reaction can be carried out by combining the compound of Formula LXIII with an alkali metal azide, for example, sodium azide, in a suitable solvent such as DMF and heating, for example to about 50 °C -60 °C, optionally in the presence of ammonium chloride. The product can be isolated from the reaction mixture using conventional methods.

In step (3) of Reaction Scheme X, an 8-nitrotetrazolo[1,5-*a*]pyridin-7-amine of Formula LXIV is reduced to provide a compound of Formula LXV. The reaction can be carried out by hydrogenation using a heterogeneous hydrogenation catalyst such as palladium on carbon or platinum on carbon. The hydrogenation is conveniently carried out in a Parr apparatus in a suitable solvent such as toluene, methanol, acetonitrile, or ethyl acetate. The reaction can be carried out at ambient temperature, and the product can be isolated using conventional methods.

In step (4) of Reaction Scheme X, a tetrazolo[1,5-*a*]pyridine-7,8-diamine of Formula LXV, is reacted with a carboxylic acid or an equivalent thereof to provide a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula LXVI. The carboxylic acid or equivalent is selected such that it will provide the desired –X-Hal substituent in a compound of Formula LXVI. The reaction can be carried out as described in step (7) of Reaction Scheme VIII. The product can be isolated using conventional methods.

In step (5) of Reaction Scheme X, a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula LXVI is treated with *N*-hydroxyphthalimide to provide a compound of Formula LXVII, which contains a *N*-phthalimide-protected hydroxylamine. The reaction is conveniently carried out as described in step (4) of Reaction Scheme I. The product or a pharmaceutically acceptable salt thereof can be isolated using conventional methods.

In step (6) of Reaction Scheme X, the *N*-phthalimide-protected hydroxylamine of Formula LXVII is treated with hydrazine in a suitable solvent such as ethanol to provide a hydroxylamine of Formula LXVIII. The reaction can be carried out at ambient temperature and the product can be isolated from the reaction mixture using conventional methods.

In step (7) Reaction Scheme X, the hydroxylamine group in a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula LXVIII reacts with an aldehyde or ketone of Formula R_2'C(O)R_2" to provide an oxime of Formula LXIX. The reaction can be carried out using the conditions described above in step (6) of Reaction Scheme I and the product can be isolated from the reaction mixture using conventional methods.

In step (8) of Reaction Scheme X, the tetrazolo ring is removed from a 7*H*-imidazo[4,5-*c*]tetrazolo[1,5-*a*]pyridine of Formula LXIX by reaction with triphenylphosphine to form an *N*-triphenylphosphinyl intermediate of Formula LXX. The reaction with triphenylphosphine can be run in a suitable solvent such as toluene or 1,2-dichlorobenzene under an atmosphere of nitrogen with heating, for example at the reflux temperature.

In step (9) of Reaction Scheme X, an *N*-triphenylphosphinyl intermediate of Formula LXX is hydrolyzed to provide an oxime-substituted 1*H*-imidazo[4,5-*c*]pyridin-4-amine of Formula LXXI. The hydrolysis can be carried out by general methods well known to those skilled in the art, for example, by heating in a lower alkanol or an alkanol/water solution in the presence of an acid such as trifluoroacetic acid, acetic acid, or hydrochloric acid. The product can be isolated from the reaction mixture using conventional methods as the compound of Formula LXXI or as a pharmaceutically acceptable salt thereof.

A compound of the Formula LXXI may also be obtained through an alternative two-step route from a compound of Formula LXVII. In step (6a) of Reaction Scheme X, a compound of Formula LXVII is treated sequentially according to the reaction conditions described in steps (8) and (9) of Reaction Scheme X using hydrochloric acid as the acid in step (9). Under these reaction conditions, the *N*-phthalimide is removed to provide the hydroxylamine-substituted 1*H*-imidazo[4,5-*c*]pyridin-4-amine of Formula LXXII. The product can be isolated and purified using conventional methods.

In step (7a) of Reaction Scheme X, a hydroxylamine-substituted 1*H*-imidazo[4,5-*c*]pyridin-4-amine of Formula LXXII reacts with an aldehyde or ketone of Formula R_2'C(O)R_2" to provide an oxime of Formula LXXI. The reaction can be carried out using the conditions described above in step (6) of Reaction Scheme I, and the product or the

pharmaceutically acceptable salt thereof can be isolated from the reaction mixture using conventional methods.

In step (10) of Reaction Scheme X, the oxime of Formula LXXI is reduced using the conditions described in step (7) of Reaction Scheme I to afford a compound of Formula LXXIII, a subgenus of Formulas I, II, and VI. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

In step (11) of Reaction Scheme X, a hydroxylamine of Formula LXXIII is converted into a compound of Formula LXXIV, a subgenus of Formulas I, II, and VI, using the reagents and conditions described in Reaction Scheme V or step (2) of Reaction Scheme VI. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

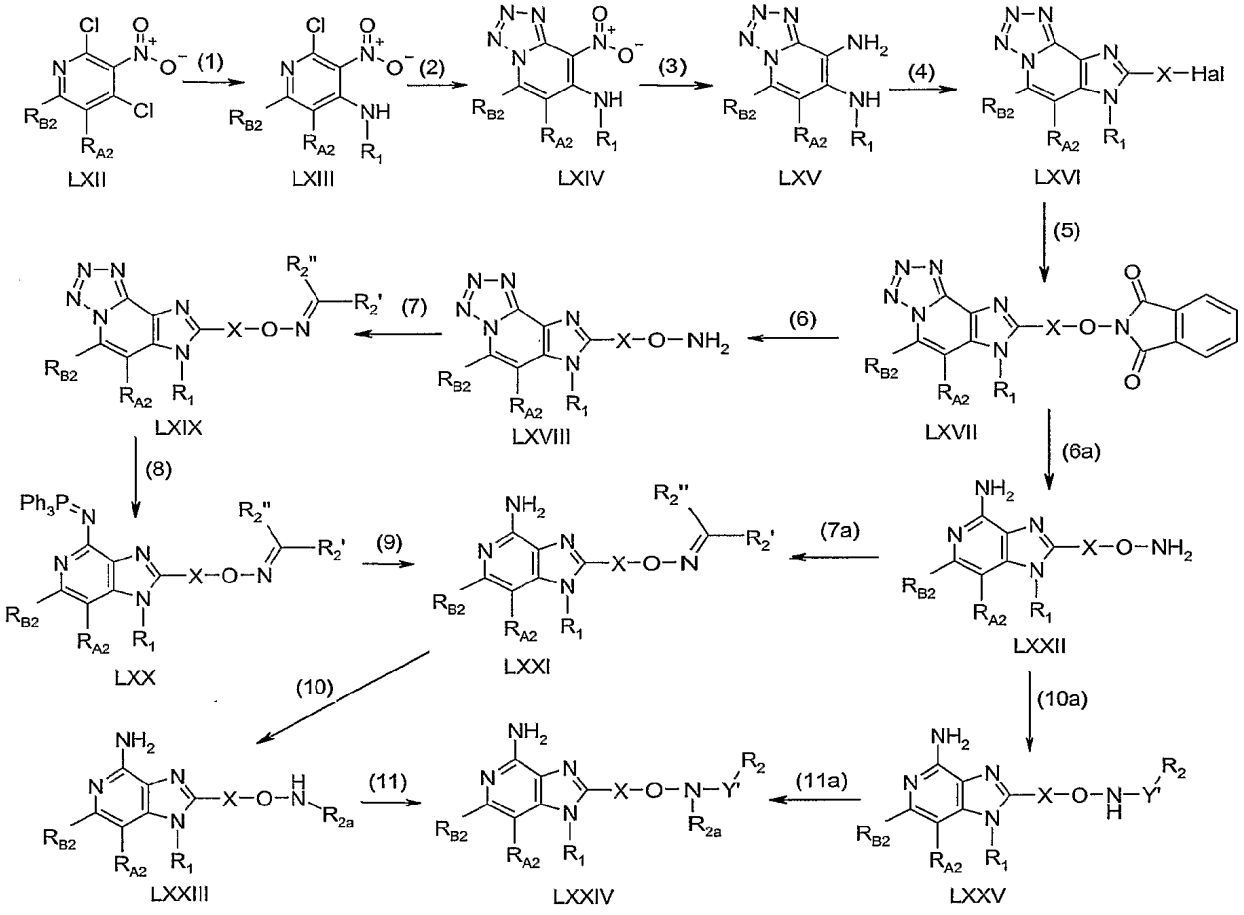
Alternatively, in steps (10a) and (11a) of Reaction Scheme X, a hydroxylamine of Formula LXXII is converted into a compound of Formula LXXIV using the reagents and methods described in steps (12a) and (13a), respectively, of Reaction Scheme VIII. The product or pharmaceutically acceptable salt thereof can be isolated by conventional methods.

For some embodiments, compounds shown in Reaction Scheme X can be further elaborated using conventional synthetic methods. For Example, amines of Formula R_1-NH_2, used in step (1) of Reaction Scheme X, may contain a protected functional group, such as a *tert*-butoxycarbonyl-protected amino group. The protecting group may be removed later in Reaction Scheme X after step (4) to reveal, for example, an amine on the R_1 group of a compound of Formula LXVI. An amino group introduced in this manner may be further functionalized by applying the chemistry described in steps (5) and (5a) of Reaction Scheme II to provide compounds of the Formula LXVI in which R_1 is –X'-N(R_8)-Q-R_4 or X'-R_{5a}, which can be converted into compounds of the Formula LXXIII or LXXIV using the chemistry described in steps (5) – (10) or (11), respectively, of Reaction Scheme X. Alternatively, the protecting group may be removed after step (7) of Reaction Scheme X to reveal an amine on the R_1 group of a compound of Formula LXIX. The amino group may be further functionalized as described above to provide compounds of the Formula LXIX in which R_1 is –X'-N(R_8)-Q-R_4 or -X'-R_{5a}, which can be converted

into compounds of the Formula LXXIII or LXXIV using the chemistry described in steps (8) - (10) or (11) of Reaction Scheme X.

Compounds of the Formula LXXIII, LXXIV, or LXXV in which R_1 is -X"-O-N=C(R_1')(R_1") or -X"-O-NR_{1a}-Y'-R_{1b} can be synthesized from compounds shown in Reaction Scheme X using the chemistry described above in association with Reaction Scheme VIII.

Reaction Scheme X



Pharmaceutical Compositions and Biological Activity

Pharmaceutical compositions of the invention contain a therapeutically effective amount of a compound or salt of the invention as described above in combination with a pharmaceutically acceptable carrier.

The terms "a therapeutically effective amount" and "effective amount" mean an amount of the compound or salt sufficient to induce a therapeutic or prophylactic effect,

such as cytokine induction, immunomodulation, antitumor activity, and/or antiviral activity. Although the exact amount of active compound or salt used in a pharmaceutical composition of the invention will vary according to factors known to those of skill in the art, such as the physical and chemical nature of the compound or salt, the nature of the carrier, and the intended dosing regimen, it is anticipated that the compositions of the invention will contain sufficient active ingredient to provide a dose of about 100 nanograms per kilogram (ng/kg) to about 50 milligrams per kilogram (mg/kg), preferably about 10 micrograms per kilogram (μg/kg) to about 5 mg/kg, of the compound or salt to the subject. A variety of dosage forms may be used, such as tablets, lozenges, capsules, parenteral formulations, syrups, creams, ointments, aerosol formulations, transdermal patches, transmucosal patches and the like.

The compounds or salts of the invention can be administered as the single therapeutic agent in the treatment regimen, or the compounds or salts of the invention may be administered in combination with one another or with other active agents, including additional immune response modifiers, antivirals, antibiotics, antibodies, proteins, peptides, oligonucleotides, etc.

Compounds or salts of the invention have been shown to induce the production of certain cytokines and certain compounds or salts of the invention may inhibit the production of certain cytokines in experiments performed according to the tests set forth below. These results indicate that the compounds or salts are useful as immune response modifiers that can modulate the immune response in a number of different ways, rendering them useful in the treatment of a variety of disorders.

Cytokines whose production may be induced by the administration of compounds or salts of the invention generally include interferon-α (IFN-α) and/or tumor necrosis factor-α (TNF-α) as well as certain interleukins (IL). Cytokines whose biosynthesis may be induced by compounds or salts of the invention include IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12, and a variety of other cytokines. Among other effects, these and other cytokines can inhibit virus production and tumor cell growth, making the compounds or salts useful in the treatment of viral diseases and neoplastic diseases. Accordingly, the invention provides a method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt or composition of the invention

to the animal. The animal to which the compound or salt or composition is administered for induction of cytokine biosynthesis may have a disease as described *infra*, for example a viral disease or a neoplastic disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

In addition to the ability to induce the production of cytokines, compounds or salts of the invention can affect other aspects of the innate immune response. For example, natural killer cell activity may be stimulated, an effect that may be due to cytokine induction. The compounds or salts may also activate macrophages, which in turn stimulate secretion of nitric oxide and the production of additional cytokines. Further, the compounds or salts may cause proliferation and differentiation of B-lymphocytes.

Compounds or salts of the invention can also have an effect on the acquired immune response. For example, the production of the T helper type 1 (T_H1) cytokine IFN-γ may be induced indirectly and the production of the T helper type 2 (T_H2) cytokines IL-4, IL-5 and IL-13 may be inhibited upon administration of the compounds or salts.

Other cytokines whose production may be inhibited by the administration of compounds or salts of the invention include tumor necrosis factor-α (TNF-α). Among other effects, inhibition of TNF-α production can provide prophylaxis or therapeutic treatment of TNF-α mediated diseases in animals, making the compounds or salt useful in the treatment of, for example, autoimmune diseases. Accordingly, the invention provides a method of inhibiting TNF-α biosynthesis in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. The animal to which the compound or salt or composition is administered for inhibition of TNF-α biosynthesis may have a disease as described *infra*, for example an autoimmune disease, and administration of the compound or salt may provide therapeutic treatment. Alternatively, the compound or salt may be administered to the animal prior to the animal acquiring the disease so that administration of the compound or salt may provide a prophylactic treatment.

Whether for prophylaxis or therapeutic treatment of a disease, and whether for effecting innate or acquired immunity, the compound or salt or composition may be

administered alone or in combination with one or more active components as in, for example, a vaccine adjuvant. When administered with other components, the compound or salt and other component or components may be administered separately; together but independently such as in a solution; or together and associated with one another such as (a) covalently linked or (b) non-covalently associated, e.g., in a colloidal suspension.

Conditions for which IRMs identified herein may be used as treatments include, but are not limited to:

(a) viral diseases such as, for example, diseases resulting from infection by an adenovirus, a herpesvirus (e.g., HSV-I, HSV-II, CMV, or VZV), a poxvirus (e.g., an orthopoxvirus such as variola or vaccinia, or molluscum contagiosum), a picornavirus (e.g., rhinovirus or enterovirus), an orthomyxovirus (e.g., influenzavirus), a paramyxovirus (e.g., parainfluenzavirus, mumps virus, measles virus, and respiratory syncytial virus (RSV)), a coronavirus (e.g., SARS), a papovavirus (e.g., papillomaviruses, such as those that cause genital warts, common warts, or plantar warts), a hepadnavirus (e.g., hepatitis B virus), a flavivirus (e.g., hepatitis C virus or Dengue virus), or a retrovirus (e.g., a lentivirus such as HIV);

(b) bacterial diseases such as, for example, diseases resulting from infection by bacteria of, for example, the genus Escherichia, Enterobacter, Salmonella, Staphylococcus, Shigella, Listeria, Aerobacter, Helicobacter, Klebsiella, Proteus, Pseudomonas, Streptococcus, Chlamydia, Mycoplasma, Pneumococcus, Neisseria, Clostridium, Bacillus, Corynebacterium, Mycobacterium, Campylobacter, Vibrio, Serratia, Providencia, Chromobacterium, Brucella, Yersinia, Haemophilus, or Bordetella;

(c) other infectious diseases, such chlamydia, fungal diseases including but not limited to candidiasis, aspergillosis, histoplasmosis, cryptococcal meningitis, or parasitic diseases including but not limited to malaria, pneumocystis carnii pneumonia, leishmaniasis, cryptosporidiosis, toxoplasmosis, and trypanosome infection;

(d) neoplastic diseases, such as intraepithelial neoplasias, cervical dysplasia, actinic keratosis, basal cell carcinoma, squamous cell carcinoma, renal cell carcinoma, Kaposi's sarcoma, melanoma, leukemias including but not limited to myelogeous leukemia, chronic lymphocytic leukemia, multiple myeloma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, B-cell lymphoma, and hairy cell leukemia, and other cancers;

(e) T_H2-mediated, atopic diseases, such as atopic dermatitis or eczema, eosinophilia, asthma, allergy, allergic rhinitis, and Ommen's syndrome;

(f) certain autoimmune diseases such as systemic lupus erythematosus, essential thrombocythaemia, multiple sclerosis, discoid lupus, alopecia areata; and

(g) diseases associated with wound repair such as, for example, inhibition of keloid formation and other types of scarring (e.g., enhancing wound healing, including chronic wounds).

Additionally, an IRM compound or salt of the present invention may be useful as a vaccine adjuvant for use in conjunction with any material that raises either humoral and/or cell mediated immune response, such as, for example, live viral, bacterial, or parasitic immunogens; inactivated viral, tumor-derived, protozoal, organism-derived, fungal, or bacterial immunogens, toxoids, toxins; self-antigens; polysaccharides; proteins; glycoproteins; peptides; cellular vaccines; DNA vaccines; autologous vaccines; recombinant proteins; and the like, for use in connection with, for example, BCG, cholera, plague, typhoid, hepatitis A, hepatitis B, hepatitis C, influenza A, influenza B, parainfluenza, polio, rabies, measles, mumps, rubella, yellow fever, tetanus, diphtheria, hemophilus influenza b, tuberculosis, meningococcal and pneumococcal vaccines, adenovirus, HIV, chicken pox, cytomegalovirus, dengue, feline leukemia, fowl plague, HSV-1 and HSV-2, hog cholera, Japanese encephalitis, respiratory syncytial virus, rotavirus, papilloma virus, yellow fever, and Alzheimer's Disease.

Certain IRM compounds or salts of the present invention may be particularly helpful in individuals having compromised immune function. For example, certain compounds or salts may be used for treating the opportunistic infections and tumors that occur after suppression of cell mediated immunity in, for example, transplant patients, cancer patients and HIV patients.

Thus, one or more of the above diseases or types of diseases, for example, a viral disease or a neoplastic disease may be treated in an animal in need thereof (having the disease) by administering a therapeutically effective amount of a compound or salt of the invention to the animal.

An amount of a compound or salt effective to induce or inhibit cytokine biosynthesis is an amount sufficient to cause one or more cell types, such as monocytes,

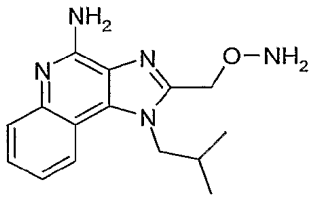
macrophages, dendritic cells and B-cells to produce an amount of one or more cytokines such as, for example, IFN-α, TNF-α, IL-1, IL-6, IL-10 and IL-12 that is increased (induced) or decreased (inhibited) over a background level of such cytokines. The precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. The invention also provides a method of treating a viral infection in an animal and a method of treating a neoplastic disease in an animal comprising administering an effective amount of a compound or salt or composition of the invention to the animal. An amount effective to treat or inhibit a viral infection is an amount that will cause a reduction in one or more of the manifestations of viral infection, such as viral lesions, viral load, rate of virus production, and mortality as compared to untreated control animals. The precise amount that is effective for such treatment will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg. An amount of a compound or salt effective to treat a neoplastic condition is an amount that will cause a reduction in tumor size or in the number of tumor foci. Again, the precise amount will vary according to factors known in the art but is expected to be a dose of about 100 ng/kg to about 50 mg/kg, preferably about 10 μg/kg to about 5 mg/kg.

Objects and advantages of this invention are further illustrated by the following examples, but the particular materials and amounts thereof recited in these examples, as well as other conditions and details, should not be construed to unduly limit this invention.

EXAMPLES

Example 1

O-{[4-Amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}hydroxylamine



Part A

N^4-(2-Methylpropyl)quinoline-3,4-diamine (41 g), dichloromethane (550 mL), triethylamine (40 mL, 1.5 eq), and chloroacetyl chloride (16.7 mL, 1.1 eq.) were combined and then stirred at ambient temperature over the weekend. The reaction mixture was diluted with 1,2-dichloroethane (75 mL) and then washed with saturated aqueous sodium bicarbonate (3 x 400 mL). The organic layer was dried over magnesium sulfate, filtered through a layer of CELITE filter aid, and then concentrated under reduced pressure to provide 52.81 g of 2-chloromethyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline as a brown solid.

Part B

3-Chloroperoxybenzoic acid (mCPBA) (16.4 g of 77% max, 73.1 mmol) was added to a solution of 2-chloromethyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline (10 g, 36.5 mmol) in chloroform (250 mL). The reaction mixture was stirred at ambient temperature overnight. Ammonium hydroxide (100 mL) was added and the reaction was stirred vigorously for 15 minutes. *Para*-toluenesulfonyl chloride (8.4 g, 43.8 mmol) was added in portions over a period of 10 minutes. The reaction mixture was stirred at ambient temperature for 1 hour and then filtered to remove a precipitate. The filtrate was transferred to a separatory funnel and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 100 mL). The combined organics were dried over magnesium sulfate, filtered through a layer of CELITE filter aid, and then concentrated under reduced pressure to provide 16 g of crude product as a yellow foam. The foam was dissolved in 10% methanol in dichloromethane (20 mL). The solution was divided and loaded onto two FLASH 40+M silica cartridges (90 g), (available from Biotage, Inc,

Charlottesville, Virginia, USA). The cartridges were eluted sequentially with 1L 1:1 ethyl acetate:hexanes, 2% methanol in 1:1 ethyl acetate:hexanes, and 5% methanol in 1:1 ethyl acetate:hexanes. The fractions containing product were combined and then concentrated under reduced pressure to provide 6.4 g of 2-chloromethyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as an orange foam.

Part C

Triethylamine (536 mg, 5.19 mmol) was added to a solution of *N*-hydroxyphthalimide (678 mg, 4.16 mmol) in *N,N*-dimethylformamide (DMF); after 5 minutes a solution of 2-chloromethyl-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (1 g) in DMF (10 mL) was added. The reaction mixture was stirred at ambient temperature for 2 hours. The reaction mixture was diluted with dichloromethane (50 mL) and then washed with water (1 x 100 mL). The aqueous layer was extracted with dichloromethane (2 x 50 mL) and ethyl acetate (1 x 50 mL). The combined organics were dried over magnesium sulfate, filtered through a layer of CELITE filter aid, and then concentrated under reduced pressure to provide 1.8 g of crude product as a yellow solid. The solid was dissolved in 5% methanol in chloroform (10 mL) and loaded onto a FLASH 40+M silica cartridge (90 g). The cartridge was eluted sequentially with 1L 1% methanol in chloroform and 3% methanol in chloroform. The fractions containing the desired product were combined and then concentrated under reduced pressure to provide 950 mg of a yellow solid. This material was recrystallized from acetonitrile, isolated by filtration, washed sequentially with acetonitrile and diethyl ether, and then dried in a vacuum oven at 65 °C overnight to provide 640 mg of 2-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}isoindole-1,3-dione as a yellow crystalline solid, mp 221-222 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.10 (d, J = 7.6 Hz, 1H), 7.88 (s, 4H), 7.63 (dd, J = 8.3 Hz, 1.2 Hz, 1H), 7.48 (m, 1H), 7.32 (m, 1H), 6.69 (br s, 2H), 5.51 (s, 2H), 4.73 (d, J = 7.6 Hz, 2H), 2.35 (m, 1H), 1.01 (d, J = 6.6 Hz, 6H);

MS (APCI) *m/z* 448.0 $(M + H)^+$;

Anal. Calc'd for $C_{23}H_{21}N_5O_3 \bullet 0.5CH_3CN \bullet 0.5H_2O$: C, 64.78; H, 5.32; N, 17.31. Found: C, 64.87; H, 5.28; N, 17.63.

Part D

Hydrazine (15 mL) was added to a solution of 2-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}isoindole-1,3-dione (51 g of crude material from a large scale reaction) in ethanol (200 mL) and a precipitate formed almost immediately. The reaction mixture was stirred at ambient temperature for 1.5 hours and then filtered. The filter cake was washed with several portions of dichloromethane. The filtrate was concentrated under reduced pressure to provide 40 g of crude product as a brown semi-solid. The solid was partitioned between 1M aqueous hydrochloric acid (300 mL) and dichloromethane (100 mL). The layers were separated. The aqueous layer was extracted with dichloromethane (2 x 100 mL). Analysis by liquid chromatography/mass spectroscopy (LCMS) showed that the organics did not contain product. The aqueous layer was made basic (pH ~10) with solid sodium carbonate and then extracted with dichloromethane (3 x 100 mL). The combined extracts were dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 9.29 g of product as a brown foam. A portion (1.7 g) of this material was purified on a FLASH 40+S silica cartridge (40 g), (available from Biotage, Inc, Charlottesville, Virginia, USA), eluting sequentially with 500 mL of 2%, 5%, 5%, and 10% methanol in ethyl acetate. The fractions containing product were combined and then concentrated under reduced pressure to provide 950 mg of an oil. The oil was dissolved in dichloromethane and then combined with 4M hydrochloric acid in dioxane. The resulting precipitate was isolated by filtration and then partitioned between dichloromethane (50 mL) and saturated aqueous sodium bicarbonate (50 mL). The aqueous layer was extracted with dichloromethane (3 x 50 mL). The combined organics were concentrated under reduced pressure to provide 500 mg of a foam. This material was dissolved in dichloromethane (50 mL) and then combined with 4M hydrochloric acid in dioxane (30 mL). A precipitate formed. The mixture was concentrated and then dissolved in hot ethanol. The solution was allowed to cool to ambient temperature, chilled (-10 °C) in a freezer overnight, and then allowed to warm to ambient temperature. A precipitate was isolated by filtration, washed with ethanol and acetonitrile, and then dried under high vacuum overnight to provide 261 mg of *O*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}hydroxylamine dihydrochloride as a white crystalline solid, mp 205-207 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.23 (d, J = 8.0 Hz, 1H), 7.86 (dd, J = 8.3 Hz, 1.0 Hz, 1H), 7.75 (dd, J = 7.3, 7.3 Hz, 1H), 7.62 (m, 1H), 5.57 (s, 2H), 4.64 (d, J = 7.6 Hz, 2H), 2.20 (m, 1H), 0.98 (d, J = 6.6 Hz, 6H);

^{13}C NMR (75 MHz, DMSO-d_6) δ 149.6, 149.2, 135.8, 134.4, 130.4, 125.5, 125.3, 122.7, 119.0, 112.9, 66.9, 52.5, 29.1, 19.3 (2);

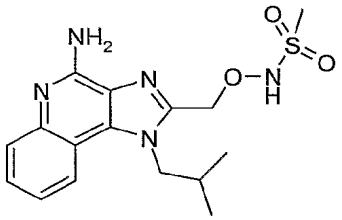
MS (APCI) *m/z* 286.1 $(M + H)^+$;

Anal. Calc'd for $C_{15}H_{19}N_5O$•2.0 HCl •0.3 H_2O: C, 49.54; H, 5.99; N, 19.26.

Found: C, 49.87; H, 6.36; N, 18.94.

Example 2

N-{[4-Amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}methanesulfonamide



Triethylamine (1.47 mL, 10.5 mmol) was added to a solution of *O*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}hydroxylamine (1.5 g, 5.3 mmol) in dichloromethane (50 mL). Methanesulfonyl chloride (0.448 mL, 5.78 mmol) was added and the reaction mixture was stirred at ambient temperature for 2 hours. The reaction mixture was washed with saturated aqueous sodium bicarbonate (1 x 30 mL) and brine (1 x 30 mL), dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 2.16 g of crude product as a brown foam. This material was dissolved in dichloromethane (10 mL) and then loaded onto a FLASH 40+S silica cartridge (40 g). The cartridge was eluted sequentially with 500 mL ethyl acetate, 2%, 3%, and 5% methanol in ethyl acetate. The fractions containing product were combined and then concentrated under reduced pressure to provide 850 mg of a yellow solid. The material was recrystallized from 3:2 ethanol:acetonitrile and dried under high vacuum to provide 206 mg of *N*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}methanesulfonamide as a yellow crystalline solid, mp 215-216 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.3 (br s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.63 (d, J = 7.4 Hz, 1H), 7.46 (m, 1H), 7.29 (m, 1H), 6.69 (br s, 2H), 5.23 (s, 2H), 4.50 (d, J = 7.6 Hz, 2H), 3.05 (s, 3H), 2.25 (m, 1H), 0.93 (d, J = 6.6 Hz, 6H);

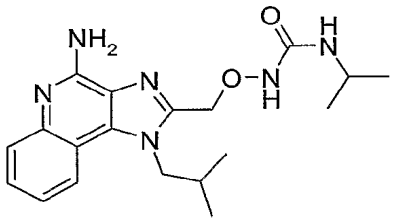
^{13}C NMR (75 MHz, DMSO-d_6) δ 152.9, 147.8, 146.3, 134.0, 127.9, 127.6, 127.3, 122.1, 121.5, 115.6, 70.9, 52.7, 37.6, 29.6, 20.1 (2);

MS (APCI) *m/z* 364.1 $(M + H)^+$;

Anal. Calc'd for $C_{16}H_{21}N_5O_3S$: C, 52.88; H, 5.82; N, 19.27. Found: C, 52.96; H, 5.81; N, 19.04.

Example 3

N-{[4-Amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}-*N'*-isopropylurea



Isopropyl isocyanate (0.620 mL, 6.31 mmol) was added to a solution of *O*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}hydroxylamine (1.5 g, 5.3 mmol) in dichloromethane (50 mL). The reaction mixture was stirred at ambient temperature for 1 hour and then concentrated under reduced pressure to provide crude product as a brown foam. This material was dissolved in dichloromethane (10 mL) and then loaded onto a FLASH 40+S silica cartridge (40 g). The cartridge was eluted sequentially with 500 mL 2%, 4%, 6%, and 8% methanol in ethyl acetate. The fractions containing product were combined and then concentrated under reduced pressure to provide 880 mg of a yellow solid. This solid was recrystallized from acetonitrile, isolated by filtration, washed with acetonitrile and diethyl ether, and then dried under high vacuum to provide 365 mg of *N*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}-*N'*-isopropylurea as a light yellow crystalline solid, mp 218-219 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 9.21 (s, 1H), 8.02 (d, J = 8.1 Hz, 1H), 7.62 (d, J = 7.4 Hz, 1H), 7.45 (dd, J = 7.3, 7.3 Hz, 1H), 7.28 (dd, J = 7.1, 7.1 Hz, 1H), 6.66 (br s, 2H), 6.49

(d, J = 8.1 Hz , 1H), 5.07 (s, 2H), 4.49 (d, J = 7.5 Hz, 2H), 3.71 (m, 1H), 2.22 (m, 1H), 1.01 (d, J = 6.5 Hz, 6H), 0.93 (d, J = 6.6 Hz, 6H);

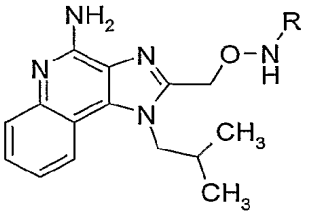
MS (APCI) *m/z* 371.1 $(M + H)^+$;

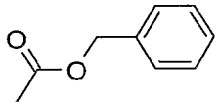
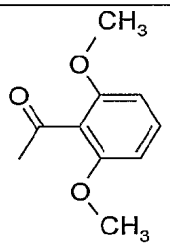
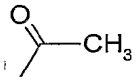
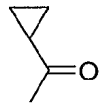
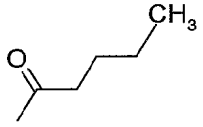
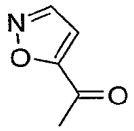
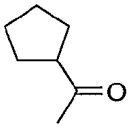
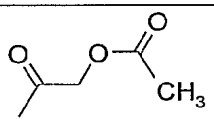
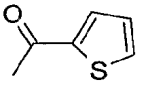
Anal. Calc'd for $C_{19}H_{26}N_6O_2$: C, 61.60; H, 7.07; N, 22.69.

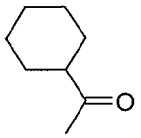
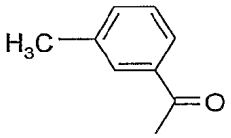
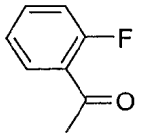
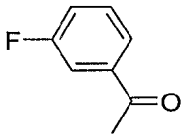
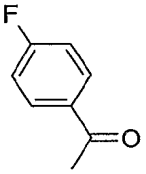
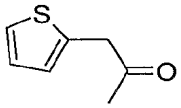
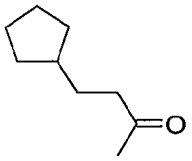
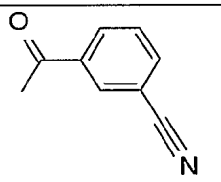
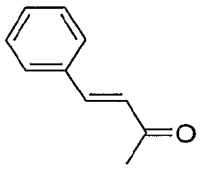
Found: C, 61.41; H, 7.40; N, 22.37.

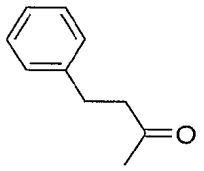
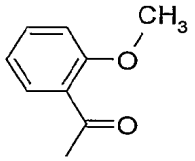
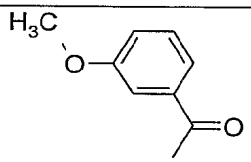
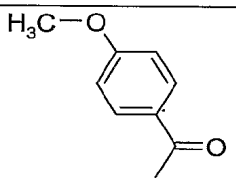
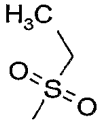
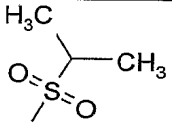
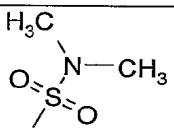
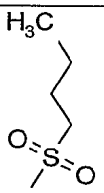
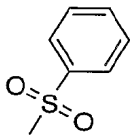
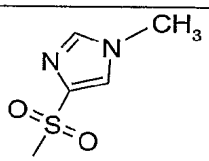
Examples 4 - 42

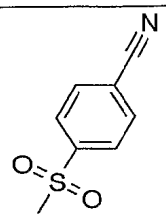
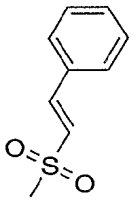
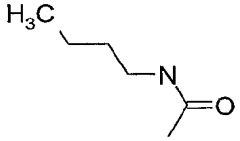
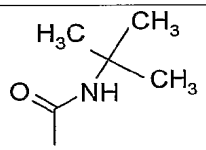
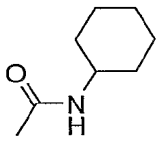
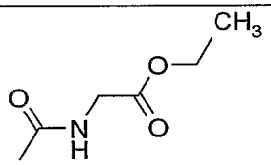
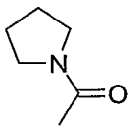
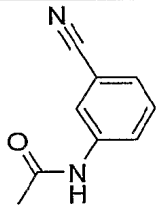
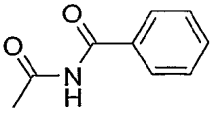
An acid chloride, sulfonyl chloride, sulfamoyl chloride, carbamoyl chloride or isocyanate from the table below (1.1 equivalents) was added to a test tube containing a solution of *O*-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-c]quinolin-2-yl]methyl}hydroxylamine (30 mg) and triethylamine (2.0 eq.) in dichloromethane (1 mL). The test tube was capped and placed on a shaker at ambient temperature overnight (approximately 18 hours). The reaction was quenched by adding 2 drops of water and then vortexing the test tube. The solvent was removed by vacuum centrifugation. The compounds were purified by preparative high performance liquid chromatography (prep HPLC) using a Waters Fraction Lynx automated purification system. The prep HPLC fractions were analyzed using a Micromass LC-TOFMS, and the appropriate fractions were centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. Column: Phenomenex LUNA C18(2), 21.2 x 50 millimeters (mm), 10 micron particle size, 100 Angstroms (Å) pore; flow rate: 25 mL/min; non-linear gradient elution from 5-95% B in 9 min, then hold at 95% B for 2 min, where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroacetic acid/acetonitrile; fraction collection by mass-selective triggering. The table below shows the acid chloride, sulfonyl chloride, sulfamoyl chloride, carbamoyl chloride or isocyanate used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

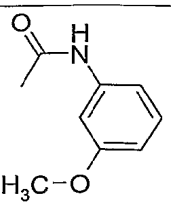
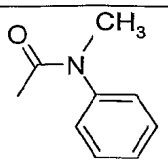


Example	Reagent	R	Measured Mass (M+H)
4	Benzyloxy chloroformate		420.2029
5	2,6-Dimethoxybenzoyl chloride		450.2139
6	Acetyl chloride		328.1793
7	Cyclopropanecarbonyl chloride		354.1964
8	Pentanoyl chloride		370.2253
9	Isoxazole-5-carbonyl chloride		381.1691
10	Cyclopentanecarbonyl chloride		382.2254
11	Acetoxyacetyl chloride		386.1861
12	Thiophene-2-carbonyl chloride		396.1524

13	Cyclohexanecarbonyl chloride		396.2410
14	*m*-Toluoyl chloride		404.2123
15	2-Fluorobenzoyl chloride		408.1862
16	3-Fluorobenzoyl chloride		408.1859
17	4-Fluorobenzoyl chloride		408.1833
18	2-Thiopheneacetyl chloride		410.1675
19	3-Cyclopentylpropionyl chloride		410.2574
20	3-Cyanobenzoyl chloride		415.1883
21	Cinnamoyl chloride		416.2099

22	Hydrocinnamoyl chloride		418.2263
23	2-Methoxybenzoyl chloride		420.2025
24	3-Methoxybenzoyl chloride		420.2057
25	4-Methoxybenzoyl chloride		420.2047
26	Ethanesulfonyl chloride		378.1633
27	Isopropylsulfonyl chloride		392.1779
28	Dimethylsulfamoyl chloride		393.1730
29	1-Butanesulfonyl chloride		406.1936
30	Benzenesulfonyl chloride		426.1626
31	1-Methylimidazole-4-sulfonyl chloride		430.1666

32	4-Cyanobenzenesulfonyl chloride		451.1553
33	*Beta*-styrenesulfonyl chloride		452.1757
34	*n*-Butyl isocyanate		385.2363
35	*Tert*-Butyl isocyanate		385.2388
36	Cyclohexyl isocyanate		411.2525
37	Ethyl isocyanatoacetate		415.2110
38	1-Pyrrolidinecarbonyl chloride		383.2214
39	3-Cyanophenyl isocyanate		430.2019
40	Benzoyl isocyanate		433.1987

41	3-Methoxyphenyl isocyanate		435.2169
42	*N*-Methyl *N*-phenylcarbamoyl chloride		419.2201

Examples 43 - 68

Part A

Triethylamine (9 mL, 64.7 mmol) was added to a solution of *tert*-butyl [3-(3-aminoquinolin-4-ylamino)propyl]carbamate (13.65 g, 43.1 mmol) in dichloromethane (150 mL). Chloroacetyl chloride (3.8 mL, 47.5 mmol) was added dropwise over a period of 10 minutes. The reaction mixture was stirred at ambient temperature over the weekend and then concentrated under reduced pressure. The residue was partitioned between ethyl acetate (100 mL) and 1:1 water:saturated aqueous sodium bicarbonate. The organic layer was washed with brine (100 mL). The combined aqueous layers were extracted with ethyl acetate (2 x 100 mL). The combined organics were dried over magnesium sulfate, filtered, and then concentrated under reduced pressure to provide 14.1 g of crude product as a brown foam. The foam was dissolved in a mixture of dichloromethane (15 mL) and methanol (0.5 mL). The solution was divided and loaded onto two FLASH 40+M silica cartridges (90 g). The cartridges were eluted sequentially with 1 L 1:1 ethyl acetate:hexanes, 5% methanol in 1:1 ethyl acetate:hexanes, and 10% methanol in 1:1 ethyl acetate:hexanes. The fractions containing product were combined and concentrated under reduced pressure to provide 8.96 g of tert-butyl [3-(2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate as a light brown foam.

Part B

3-Chloroperoxybenzoic acid (13.3 g of 77% max, 59.4 eq.) was added in portions over a period of 5 minutes to a solution of *tert*-butyl [3-(2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate (8.9 g, 23.7 mmol) in chloroform (200 mL). The reaction mixture was allowed to stir at ambient temperature overnight. Ammonium

hydroxide (50 mL) was added and the reaction mixture was stirred vigorously. *Para*-toluensulfonyl chloride (5.43 g, 28.5 mmol) was added over a period of 5 minutes. The reaction mixture was stirred at ambient temperature for 2 hours; an additional 1 g of *para*-toluensulfonyl chloride was added and the reaction mixture was stirred for another hour. The reaction mixture was filtered to remove solids. The filtrate was transferred to a separatory funnel and the layers were separated. The organic layer was washed with 1:1 water:saturated aqueous sodium bicarbonate (2 x 150 mL). The combined aqueous was extracted with dichloromethane (2 x 150 mL) and ethyl acetate (1 x 100 mL). The combined organic extracts were concentrated under reduced pressure to provide 13.6 g of crude product as a brown foam. The foam was dissolved in dichloromethane (20 mL). The solution was divided and loaded onto two FLASH 40+M silica cartridges (90 g). The first cartridge was eluted sequentially with 1L 1:1 ethyl acetate:hexanes, 5% methanol in 1:1 ethyl acetate:hexanes, and 10% methanol in 1:1 ethyl acetate:hexanes. The second cartridge was eluted sequentially with 1L 1:1 ethyl acetate:hexanes, 7% methanol in 1:1 ethyl acetate:hexanes, and 7% methanol in 1:1 ethyl acetate:hexanes. The fractions containing product were combined and then concentrated under reduced pressure to provide 4.3 g of *tert*-butyl [3-(4-amino-2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate as a light yellow foam.

Part C

Triethylamine (4.6 mL, 33.1 mmol) was added to a solution of *N*-hydroxyphthalimide (2.16 g, 13.2 mmol) in DMF (10 mL). A solution of *tert*-butyl [3-(4-amino-2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate (4.3 g, 11.0 mmol) in DMF (20 ml) was added. The reaction was stirred at ambient temperature for 3.5 hours and then diluted with water (100 mL). The resulting precipitate was isolated by filtration, washed with water, and then dried in a vacuum oven at 60°C over the weekend to provide 4.25 g of *tert*-butyl (3-{4-amino-2-[(1,3-dioxo-1,3-dihydroisoindol-2-yl)oxymethyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}propyl)carbamate as a light yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.2 (d, J = 8.0 Hz, 1H), 7.9 (s, 4H), 7.7 (m, 1H), 7.5 (m, 1H), 7.3 (m, 1H), 7.2 (m, 1H), 6.7 (br s, 2H), 5.5 (s, 2H), 4.8 (m, 2H), 3.2 (m, 2H), 2.2 (m, 2H), 1.4 (s, 9H);

MS (APCI) m/z 517.3 $(M + H)^+$.

Part D

Hydrazine hydrate (8 mL of 55%) was added to a suspension of *tert*-butyl (3-{4-amino-2-[(1,3-dioxo-1,3-dihydroisoindol-2-yl)oxymethyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}propyl)carbamate (4.25 g, 8.23 mmol) in ethanol (70 mL). The reaction became homogeneous after about 2 minutes. A precipitate started forming after about 1 hour. After stirring at ambient temperature for a total of 2 hours the reaction mixture was filtered and the filter cake was washed with dichloromethane. The filtrate was concentrated under reduced pressure. The residue was azeotroped twice with toluene to provide 3.63 g of *tert*-butyl [3-(4-amino-2-aminooxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate as a white solid.

Part E

Acetone (20 mL) was added to a solution of *tert*-butyl [3-(4-amino-2-aminooxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate (3.6 g) in methanol (70 mL). The reaction mixture was stirred at ambient temperature overnight and then concentrated under reduced pressure to provide 4.12 g of *tert*-butyl [3-(4-amino-2-isopropylideneaminoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate as a light yellow foam.

Part F

Trifluoroacetic acid (7 mL) was added to a suspension of *tert*-butyl [3-(4-amino-2-isopropylideneaminoxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)propyl]carbamate (4.12 g) in dichloromethane (70 mL). The reaction became homogeneous and was stirred at ambient temperature for 2.5 hours. More trifluoroacetic acid (10 mL) was added and the reaction was stirred for another hour. The reaction mixture was concentrated under reduced pressure and placed under high vacuum overnight to provide 7.68 g of propan-2-one O-{[4-amino-1-(3-aminopropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}oxime a white solid. Based on the weight this material was assumed to contain 5 equivalents of trifluoroacetic acid.

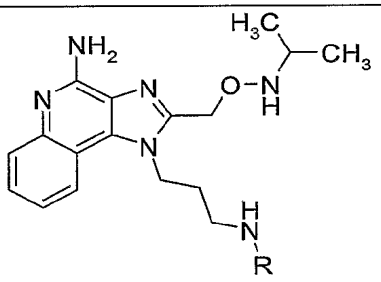
Part G

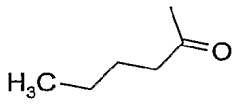
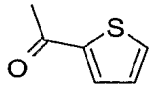
An acid chloride, sulfonyl chloride, sulfamoyl chloride, carbamoyl chloride or isocyanate from the table below (1.1 equivalents) was added to a test tube containing propan-2-one O-{[4-amino-1-(3-aminopropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-

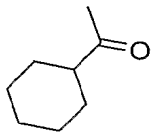
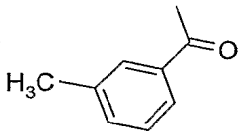
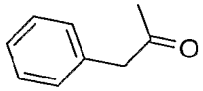
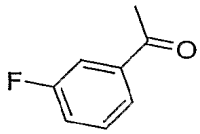
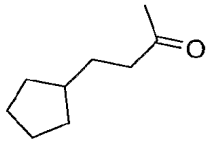
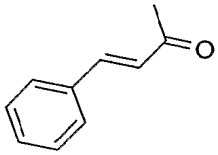
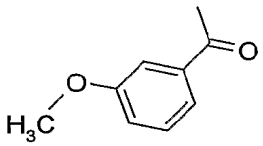
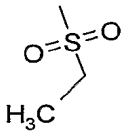
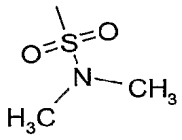
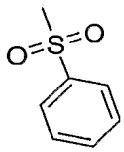
yl]methyl}oxime trifluoroacetate (~90 mg) prepared in Part F, *N,N*-diisopropylethylamine (350 µL, 10 equivalents), and chloroform (2 mL). The test tube was capped and placed on a shaker at ambient temperature overnight (approximately 18 hours). Water (1 drop) was added to the test tube and then the solvent was removed by vacuum centrifugation. The residue was dissolved in methanol (5 mL).

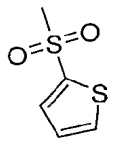
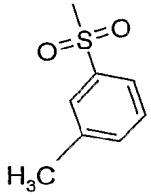
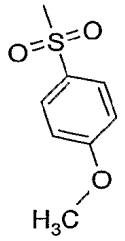
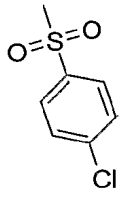
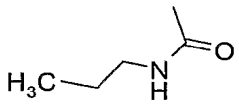
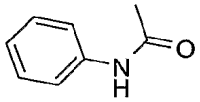
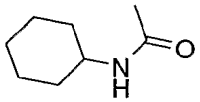
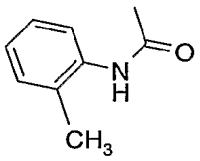
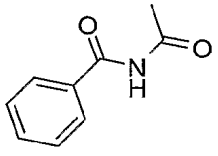
Part H

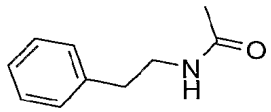
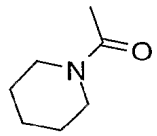
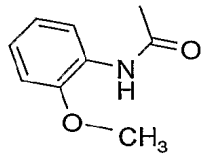
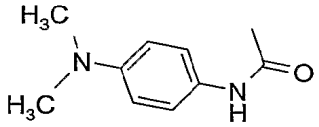
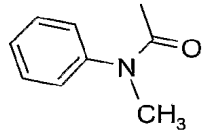
A portion (2.5 mL) of the solution from Part G was transferred to a fresh test tube and then the solvent was removed by vacuum centrifugation. Methanol (1 mL), glacial acetic acid (1 mL), and 400 µL of a 1.0 M solution of sodium cyanoborohydride in tetrahydrofuran were added to the test tube. The test tube was capped and placed on a shaker at ambient temperature overnight (approximately 18 hours). The solvent was removed by vacuum centrifugation. The compounds were purified by preparative high performance liquid chromatography (prep HPLC) using a Waters Fraction Lynx automated purification system using the method described above for Examples 4 - 42. The table below shows the acid chloride, sulfonyl chloride, sulfamoyl chloride, carbamoyl chloride or isocyanate used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



Example	Reagent	R	Measured Mass (M+H)
43	Pentanoyl chloride		413.2688
44	Thiophene-2-carbonyl chloride		439.1887

45	Cyclohexanecarbonyl chloride		439.2802
46	*m*-Toluoyl chloride		447.2496
47	Phenylacetyl chloride		447.2506
48	3-Fluorobenzoyl chloride		451.2300
49	3-Cyclopentanepropionyl chloride		453.2965
50	Cinnamoyl chloride		459.2536
51	*m*-Anisoyl chloride		463.2481
52	Ethanesulfonyl chloride		421.2022
53	Dimethylsulfamoyl chloride		436.2159
54	Benzenesulfonyl chloride		469.2024

55	2-Thiophenesulfonyl chloride		475.1577
56	3-Methylbenzenesulfonyl chloride		483.2185
57	4-Methoxybenzenesulfonyl chloride		499.2121
58	4-Chlorobenzensulfonyl chloride		503.1618
59	*n*-Propyl isocyanate		414.2620
60	Phenyl isocyanate		448.2486
61	Cyclohexyl isocyanate		454.2916
62	*o*-Tolyl isocyanate		462.2619
63	Benzoyl isocyanate		476.2406

64	2-Phenylethyl isocyanate		476.2772
65	1-Piperidinecarbonyl chloride		440.2767
66	2-Methoxyphenyl isocyanate		478.2539
67	4-Dimethylaminophenyl isocyanate		491.2894
68	*N*-Methyl *N*-phenylcarbamoyl chloride		462.2595

Examples 69 - 97

Part A

Using the general method of Examples 43 - 68 Part A, *tert*-butyl [2-(3-aminoquinolin-4-ylamino)ethyl]carbamate (43.5 g, 144 mmol) was reacted with chloroacetyl chloride (17.72 g, 158 mmol) to provide 37.39 g of *tert*-butyl [2-(2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate.

Part B

Using the general method of Examples 43 - 68 Part B, a solution of *tert*-butyl [2-(2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate (27.45 g, 76.1 mmol) in chloroform (500 mL) was treated with 3-chloroperoxybenzoic acid (25.6 g of 77% max, 114 mmol) and the resulting 5-oxide was aminated using ammonium hydroxide (150 mL) and *para*-toluenesulfonyl chloride (17.4 g, 91.3 mmol) to provide 41.83 g of crude *tert*-butyl [2-(4-amino-2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate as a brown solid. A portion (~32 g) of the crude material was dissolved in dichloromethane and then washed with 1 N hydrochloric acid (x3). The organic layer was allowed to stand

for several days and a precipitate formed. This material was isolated by filtration to provide 7.0 g of *tert*-butyl [2-(4-amino-2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate as an off white solid.

Part C

Using the general method of Examples 43 - 68 Part C, *tert*-butyl [2-(4-amino-2-chloromethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate (7 g, 19 mmol)) was reacted with *N*-hydroxyphthalimide (3.65 g, 22.3 mmol) to provide 6.37 g of *tert*-butyl (2-{4-amino-2-[(1,3-dioxo-1,3-dihydroisoindol-2-yl)oxymethyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}ethyl)carbamate as a yellow solid.

^{1}H NMR (300 MHz, DMSO-d_6) δ 8.3 (d, J = 8.5 Hz, 1H), 7.9 (s, 4H), 7.6 (m, 1H), 7.5 (m, 1H), 7.3 (m, 1H), 7.1 (m, 1H), 6.6 (br s, 2H), 5.5 (s, 2H), 4.9 (m, 2H), 3.6 (m, 2H), 1.3 (s, 9H);

MS (APCI) m/z 503.2 $(M + H)^+$.

Part D

Using the general method of Examples 43 - 68 Part D, the *N*-phthalimide protecting group was removed from *tert*-butyl (2-{4-amino-2-[(1,3-dioxo-1,3-dihydroisoindol-2-yl)oxymethyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}ethyl)carbamate (6.35 g) to provide crude *tert*-butyl [2-(4-amino-2-aminooxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate.

Part E

Acetone (25 mL) was added to a suspension of the crude material from Part D in methanol (100 mL). The resulting solution was stirred at ambient temperature for 3 hours and then concentrated under reduced pressure. The residue was azeotroped once with toluene, slurried with ethanol (100 mL) and then filtered. The filter cake was washed with additional ethanol. The filtrate was concentrated under reduced pressure to provide 3.9 g of product as a yellow solid. Additional product (0.9 g) was obtained by extracting the filter cake with dichloromethane. The two lots were combined to provide 4.8 g of *tert*-butyl [2-(4-amino-2-isopropylideneaminooxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate.

Part F

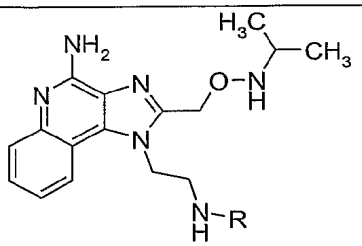
Trifluoroacetic acid (10 mL) was added to a suspension of *tert*-butyl [2-(4-amino-2-isopropylideneaminooxymethyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)ethyl]carbamate (4.8 g) in dichloromethane (100 mL). The reaction became homogeneous and was stirred at ambient temperature. At 2.5 hours and 3.5 hours more trifluoroacetic acid (10 mL and 5 mL respectively) was added. After a total reaction time of 4 hours the reaction mixture was concentrated under reduced pressure. The residue was azeotroped with toluene (x3) and then placed under high vacuum overnight to provide 9.97 g of propan-2-one *O*-{[4-amino-1-(2-aminoethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}oxime as a yellow solid. Based on the weight this material was assumed to contain 5 equivalents of trifluoroacetic acid.

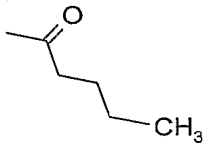
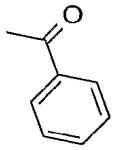
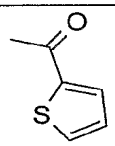
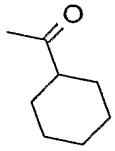
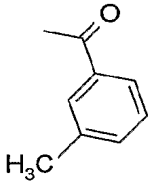
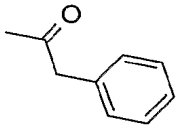
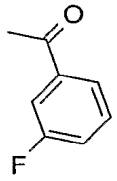
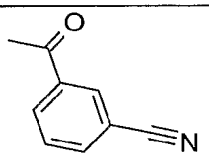
Part G

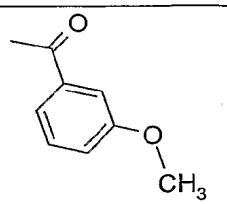
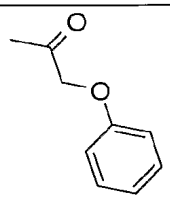
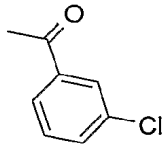
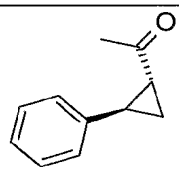
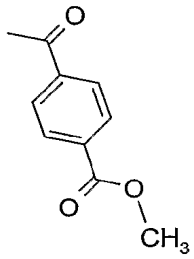
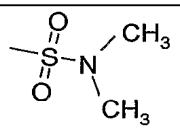
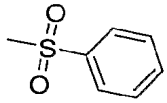
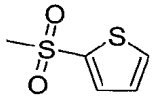
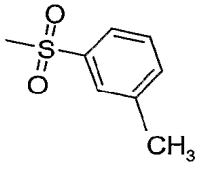
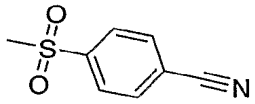
An acid chloride, sulfonyl chloride, sulfamoyl chloride, carbamoyl chloride or isocyanate from the table below (1.1 equivalents) was added to a test tube containing propan-2-one *O*-{[4-amino-1-(2-aminoethyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}oxime trifluoroacetate (~90 mg) prepared in Part F, *N*,*N*-diisopropylethylamine (350 µL, 10 equivalents), and chloroform (2 mL). The test tube was capped and placed on a shaker at ambient temperature overnight (approximately 18 hours).

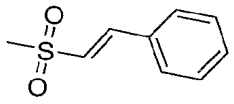
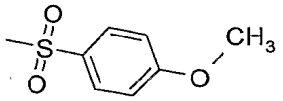
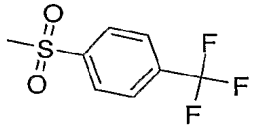
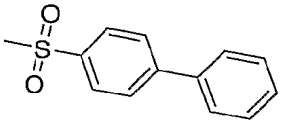
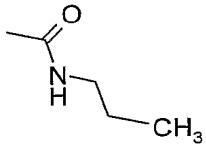
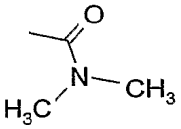
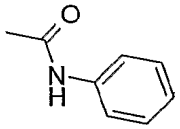
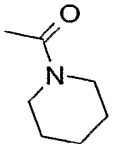
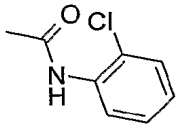
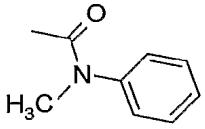
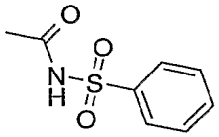
Part H

A portion (1 mL) of the solution from Part G was transferred to a fresh test tube and then the solvent was removed by vacuum centrifugation. Methanol (1 mL), glacial acetic acid (1 mL), and 300 µL of a 1.0 M solution of sodium cyanoborohydride in tetrahydrofuran were added to the test tube. The test tube was capped and placed on a shaker at ambient temperature overnight (approximately 18 hours). The solvent was removed by vacuum centrifugation. The compounds were purified by preparative high performance liquid chromatography (prep HPLC) using a Waters Fraction Lynx automated purification system using the method described above for Examples 4 - 42. The table below shows the acid chloride, sulfonyl chloride, sulfamoyl chloride, carbamoyl chloride or isocyanate used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.



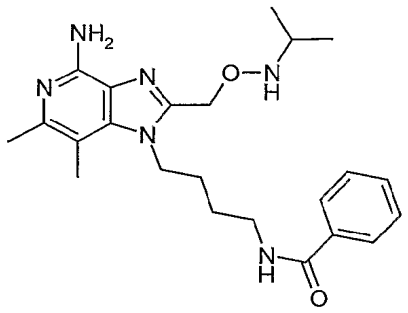
Example	Reagent	R	Measured Mass (M+H)
69	Pentanoyl chloride		399.2517
70	Benzoyl chloride		419.2220
71	Thiophene-2-carbonyl chloride		425.1739
72	Cyclohexanecarbonyl chloride		425.2692
73	*m*-Toluoyl chloride		433.2369
74	Phenylacetyl chloride		433.2391
75	3-Fluorobenzoyl chloride		437.2117
76	3-Cyanobenzoyl chloride		444.2170

77	*m*-Anisoyl chloride		449.2313
78	Phenoxyacetyl chloride		449.2321
79	3-Chlorobenzoyl chloride		453.1832
80	*Trans*-2-Phenyl-1-cyclopropanecarbonyl chloride		459.2547
81	Methyl 4-chlorocarbonyl benzoate		477.2285
82	Dimethylsulfamoyl choride		422.1976
83	Benzenesulfonyl chloride		455.1888
84	2-Thiophenesulfonyl chloride		461.1451
85	3-Methylbenzenesulfonyl chloride		469.2006
86	4-Cyanobenzenesulfonyl chloride		480.1805

87	*Beta*-Styrenesulfonyl chloride		481.2017
88	4-Methoxybenzenesulfonyl chloride		485.1993
89	4-Trifluoromethyl benzenesulfonyl chloride		523.1732
90	4-Biphenylsulfonyl chloride		531.2167
91	*n*-Propyl isocyanate		400.2466
92	*N*,*N*-Dimethylcarbamoyl chloride		386.2315
93	Phenyl isocyanate		434.2301
94	1-Piperidinecarbonyl chloride		426.2625
95	2-Chlorophenyl isocyanate		468.1926
96	*N*-Methyl *N*-phenylcarbamoyl chloride		448.2464
97	Benzenesulfonyl isocyanate		498.1898

Example 98

N-[4-(4-Amino-2-{[(isopropylamino)oxy]methyl}-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]benzamide



Part A

A solution of *tert*-butyl 4-aminobutylcarbamate (8.50 g, 45.2 mmol) in DMF (20 mL) in an addition funnel was added over 1 hour to a stirred solution of 2,4-dichloro-5,6-dimethyl-3-nitropyridine (10.0 g, 45.2 mmol) and triethylamine (9.30 mL, 67.8 mmol) in DMF (100 mL). The addition funnel was rinsed with DMF (17 mL) and the solution was added to the reaction vessel. After the reaction solution was stirred overnight at room temperature, additional *tert*-butyl 4-aminobutylcarbamate (0.1 equivalent) was added. The solution was allowed to stir an additional 2 hours, then was concentrated under reduced pressure. The resulting oil was partitioned between ethyl acetate (400 mL) and water (100 mL). The organic phase was washed with water (4 x 50 mL), then was dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel, elution with 33% ethyl acetate in hexanes followed by 66% ethyl acetate in hexanes) to afford 9.2 g of *tert*-butyl 4-[(2-chloro-5,6-dimethyl-3-nitropyridin-4-yl)amino]butylcarbamate.

Part B

The purified *tert*-butyl 4-[(2-chloro-5,6-dimethyl-3-nitropyridin-4-yl)amino]butylcarbamate from A was combined with crude *tert*-butyl 4-[(2-chloro-5,6-dimethyl-3-nitropyridin-4-yl)amino]butylcarbamate from a similar experiment to yield 38 g (approximately 101 mmol) of material, which was combined with sodium azide (13.0 g, 202 mmol), cerium(III) chloride heptahydrate (19.0 g, 51.0 mmol), and 9:1 acetontrile/water (300 mL). The reaction mixture was heated at reflux for 3 days, then was

allowed to cool to room temperature and was filtered. The filter cake was rinsed with DMF. The filtrate was concentrated under reduced pressure to yield an oil that was purified by flash chromatography (silica gel, elution with 2:1:1 ethyl acetate/hexanes/chloroform, followed by 4:1 ethyl acetate/chloroform) to afford 23 g of *tert*-butyl 4-[(5,6-dimethyl-8-nitrotetraazolo[1,5-*a*]pyridin-7-yl)amino]butylcarbamate.

Part C

A mixture of *tert*-butyl 4-[(5,6-dimethyl-8-nitrotetraazolo[1,5-*a*]pyridin-7-yl)amino]butylcarbamate (9.00 g, 23.7 mmol), 10% palladium on carbon (900 mg), and acetontrile (100 mL) was hydrogenated on a Parr apparatus for 5 hours. The mixture was filtered through CELITE filter agent, which was rinsed afterwards with methanol. The filtrate was concentrated under reduced pressure to yield 6.70 g of *tert*-butyl 4-[(8-amino-5,6-dimethyltetraazolo[1,5-*a*]pyridin-7-yl)amino]butylcarbamate.

Part D

Ethyl 2-chloroethanimidoate hydrochloride (ethyl chloroacetimidate hydrochloride) (2.58 g, 16.4 mmol) was added to a solution of *tert*-butyl 4-[(8-amino-5,6-dimethyltetraazolo[1,5-*a*]pyridin-7-yl)amino]butylcarbamate (3.80 g, 10.9 mmol) in chloroform (75 mL). The solution was stirred for 3 days, then saturated aqueous sodium bicarbonate (40 mL) was added. The aqueous phase was extracted with chloroform (3 x 40 mL). The organic phases were combined, washed with water (2 x 20 mL) and saturated aqueous sodium bicarbonate (20 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 4.3 g of *tert*-butyl 4-[8-(chloromethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butylcarbamate, which was used in the next step without purification.

Part E

Concentrated hydrochloric acid (10 mL) was added to a suspension of *tert*-butyl 4-[8-(chloromethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butylcarbamate (1.00 g, 2.30 mmol) in methanol (23 mL). The reaction mixture was stirred at room temperature for 2 hours, then was concentrated under reduced pressure to

yield a residue. The residue was concentrated twice from toluene to remove residual water, then was triturated with methanol. A solid was isolated by filtration and was dried under vacuum to provide 0.68 g of 4-[8-(chloromethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butan-1-amine hydrochloride.

Part F

Benzoic anhydride (3.1 g, 13.8 mmol) was added to a flask containing 4-[8-(chloromethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butan-1-amine hydrochloride (4.30 g, 12.5 mmol), triethylamine (3.70 mL, 26.3 mmol), and dichloromethane (100 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 day and additional triethylamine (0.5 mL) and benzoic anhydride (0.8 g) were added. The reaction mixture was stirred for 6 hours at room temperature. The volatiles were removed under reduced pressure and water (50 mL) followed by ethyl acetate (50 mL) were added to the solid residue. The mixture was sonicated for 1 minute, then the solid was isolated by filtration, washed with water and ethyl acetate, and dried under vacuum to afford 4.7 g of *N*-{4-[8-(chloromethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}benzamide.

Part G

N-Hydroxyphthalimide (2.60 g, 16.0 mmol) and triethylamine (2.20 mL, 16.0 mmmol) were added to a suspension of *N*-{4-[8-(chloromethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}benzamide (4.70 g, 11.4 mmol) in DMF (285 mL). The reaction mixture was allowed to stir for 3 days, then was concentrated under reduced pressure to a white slurry. Methanol was added and a white solid was isolated by filtration, washed with methanol, and dried under vacuum to afford 5.70 g of *N*-[4-(8-{[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)oxy]methyl}-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butyl]benzamide.

Part H

Anhydrous hydrazine (0.47 mL, 15 mmol) was added to a stirred suspension of *N*-[4-(8-{[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)oxy]methyl}-5,6-dimethyl-7*H*-

imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butyl]benzamide (2.8 g, 5.0 mmol) in ethanol (50 mL). After two hours, a solid was isolated by filtration and the filter cake was washed with ethanol. Acetone (25 mL) and methanol (25 mL) were added to the solid and the mixture was stirred overnight. The volatiles were removed under reduced pressure to afford a solid that was triturated with 1 M aqueous sodium hydroxide (10 mL) and 1:1 methanol/acetone (4 mL). The solid was isolated by filtration, washed with water, and dissolved in chloroform (100 mL). The solution was dried over magnesium sulfate, filtered, concentrated under reduced pressure, and dried under vacuum to afford 1.9 g of a *N*-{4-[5,6-dimethyl-8-({[(1-methylethylidene)amino]oxy}methyl)-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}benzamide as a white solid.

Part I

A mixture of *N*-{4-[5,6-dimethyl-8-({[(1-methylethylidene)amino]oxy}methyl)-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}benzamide (1.9 g, 4.2 mmol), triphenylphosphine (2.2 g, 8.4 mmol), and 1,2-dichlorobenzene (40 mL) was heated at 125 °C for 2 days. The reaction was allowed to cool to room temperature and was concentrated under reduced pressure. The residue was dissolved in methanol (20 mL) and 1 M aqueous hydrochloric acid (20 mL) and heated at 40 °C for 6 hours. The reaction was allowed to stand at room temperature overnight and a white precipitate formed that was removed by filtration. The filtrate was concentrated under reduced pressure and the residue was partitioned between 1 M aqueous hydrochloric acid (20 mL) and chloroform (10 mL). The aqueous layer was extracted with chloroform (3 x 10 mL). The organic layers were combined, washed with saturated aqueous sodium carbonate, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The solid was purified by chromatography using a HORIZON HPFC system (an automated, modular high-performance flash purification product available from Biotage, Inc, Charlottesville, Virginia, USA) (silica gel, gradient elution with 10-35% CMA in chloroform, where CMA is 80:18:2 chloroform/methanol/concentrated ammonium hydroxide). The appropriate fractions were combined and concentrated under reduced pressure. The solid was triturated with ethyl acetate and was isolated by filtration, washed with ethyl acetate, and dried under vacuum at 50 °C overnight to provide 0.85 g of *N*-{4-[4-amino-6,7-dimethyl-

2-({[(1-methylethylidene)amino]oxy}methyl)-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}benzamide as a white powder, mp 206.0-208.0 °C. Anal. Calcd for $C_{23}H_{30}N_6O_2 \cdot 0.06\ CHCl_3$: C, 64.46; H, 7.05; N, 19.56; Found: C, 64.31; H, 7.06; N, 19.55.

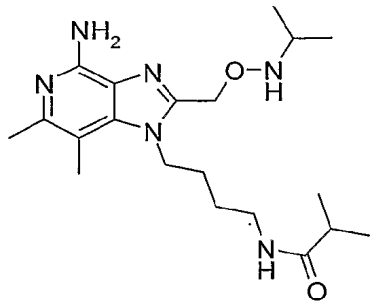
Part J

A solution of sodium cyanoborohydride in tetrahydrofuran (1 M, 6 mL) was added to a solution of *N*-{4-[4-amino-6,7-dimethyl-2-({[(1-methylethylidene)amino]oxy}methyl)-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}benzamide (260 mg, 0.62 mmol) in 1:2 acetic acid/methanol (9 mL). The reaction mixture was stirred overnight, concentrated under reduced pressure, and partitioned between 1 M aqueous hydrochloric acid (20 mL) and chloroform (5 mL). After the bubbling subsided, the layers were separated and the aqueous phase was washed with chloroform (2 x 5 mL). The organic layers were combined and back-extracted with 1 M aqueous hydrochloric acid (2 x 5 mL). The aqueous layers were combined and adjusted to pH 10 with 1 M aqueous sodium hydroxide, then were extracted with chloroform (4 x). The organic layers were combined, washed with saturated aqueous sodium bicarbonate (5 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure to yield a foam. The foam was purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with 3-35% CMA in chloroform) followed by crystallization from acetonitrile. The crystals were isolated by filtration and dried under vacuum at 70 °C to yield 80 mg of *N*-[4-(4-amino-2-{[(isopropylamino)oxy]methyl}-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]benzamide as a white powder, mp 161.0-162.0 °C.

Anal. Calcd for $C_{23}H_{32}N_6O_2$: C, 65.07; H, 7.60; N, 19.80; Found: C, 64.85; H, 7.92; N, 20.00.

Example 99

N-[4-(4-Amino-2-{[(isopropylamino)oxy]methyl}-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-2-methylpropanamide



Part A

Isobutyric anhydride (2.28 mL, 13.8 mmol) was added to a flask containing 4-[8-(chloromethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butan-1-amine hydrochloride (prepared as described in Parts A-E of Example 98, 4.30 g, 12.5 mmol), triethylamine (3.66 mL, 26.3 mmol), and dichloromethane (100 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 hours. The solution was concentrated under reduced pressure and water (50 mL) followed by ethyl acetate (50 mL) were added to the solid residue. The mixture was sonicated for 1 minute, then the solid was isolated by filtration, washed with water and ethyl acetate. Toluene was added to the solid and the mixture was concentrated under reduced pressure. The solid was dried under vacuum to afford 4.12 g of *N*-{4-[8-(chloromethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}-2-methylpropanamide.

Part B

The general method described in Part G of Example 98 was used to convert 4.10 g *N*-{4-[8-(chloromethyl)-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}-2-methylpropanamide into 4.92 g of *N*-[4-(8-{[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)oxy]methyl}-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butyl]-2-methylpropanamide.

Part C

Anhydrous hydrazine (0.91 mL, 29 mmol) was added to a stirred suspension of *N*-[4-(8-{[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)oxy]methyl}-5,6-dimethyl-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl)butyl]-2-methylpropanamide (4.90 g, 9.71 mmol) in ethanol (100 mL). Dichloromethane (50 mL) was added. After four hours, acetone (50 mL) was added and the reaction mixture was stirred overnight. A solid was removed by filtration and washed with methanol. The filtrate was concentrated to provide a solid that was triturated with 1:1 saturated aqueous sodium bicarbonate/water. The solid was isolated by filtration, washed with water, and dissolved in chloroform (300 mL). The solution was washed with water (2 x 50 mL), dried over sodium sulfate, filtered, concentrated under reduced pressure, and dried under vacuum to afford *N*-{4-[5,6-dimethyl-8-({[(1-methylethylidene)amino]oxy}methyl)-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}-2-methylpropanamide that was used in the next experiment.

Part D

A mixture of *N*-{4-[5,6-dimethyl-8-({[(1-methylethylidene)amino]oxy}methyl)-7*H*-imidazo[4,5-*c*]tetraazolo[1,5-*a*]pyridin-7-yl]butyl}-2-methylpropanamide (from Part C, approximately 9.71 mmol), triphenylphosphine (5.1 g, 19 mmol), and 1,2-dichlorobenzene (97 mL) was heated at 125 °C for 2 days, then stirred at room temperature for 3 days, then heated at 130 °C for 5 hours. The reaction was allowed to cool to room temperature and was concentrated under reduced pressure. The residue was dissolved in methanol (80 mL) and 1 M aqueous hydrochloric acid (40 mL) and heated at 40 °C for 6 hours. The reaction was allowed to stir at room temperature overnight and a white precipitate formed that was removed by filtration. The filtrate was concentrated under reduced pressure and the residue was partitioned between 1 M aqueous hydrochloric acid (20 mL) and chloroform (10 mL). The aqueous layer was extracted with chloroform (3 x 10 mL). The organic layers were combined, washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated under reduced pressure. The solid was purified by chromatography using a HORIZON HPFC system (silica gel, gradient elution with 5-55% CMA in chloroform). The appropriate fractions were combined and concentrated under reduced pressure. The resulting solid was triturated

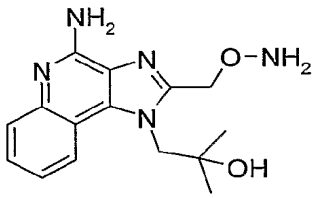
with acetonitrile and then was recrystallized from acetonitrile to provide *N*-{4-[4-amino-6,7-dimethyl-2-({[(1-methylethylidene)amino]oxy}methyl)-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}-2-methylpropanamide as a white powder, mp 180.0-181.0 °C. Anal. Calcd for $C_{20}H_{32}N_6O_2$: C, 61.83; H, 8.30; N, 21.63; Found: C, 61.65; H, 8.65; N, 21.70.

Part E

A modification on the method described in Part J of Example 98 was used to convert 1.10 g of *N*-{4-[4-amino-6,7-dimethyl-2-({[(1-methylethylidene)amino]oxy}methyl)-1*H*-imidazo[4,5-*c*]pyridin-1-yl]butyl}-2-methylpropanamide into 0.052 g of *N*-[4-(4-amino-2-{[(isopropylamino)oxy]methyl}-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-2-methylpropanamide. After the work-up, the crude material was not purified by chromatography, rather by trituration with acetonitrile. The purified product was isolated by filtration and was dried under vacuum to afford *N*-[4-(4-amino-2-{[(isopropylamino)oxy]methyl}-6,7-dimethyl-1*H*-imidazo[4,5-*c*]pyridin-1-yl)butyl]-2-methylpropanamide as a white powder, mp 156.0-157.0 °C. Anal. Calcd for $C_{20}H_{34}N_6O_2 \cdot 0.2\ H_2O \cdot 0.03\ CH_3CN$: C, 60.91; H, 8.80; N, 21.38; Found: C, 60.94; H, 9.20; N, 21.77.

Example 100

1-{4-Amino-2-[(aminooxy)methyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}-2-methylpropan-2-ol



Part A

Triethylamine (50.0 mL, 360 mmol) was added to a suspension of 4-chloro-3-nitroquinoline (50.0 g, 240 mmol) in DMF (200 mL), followed by dropwise addition of a solution of 1-amino-2-methyl-propan-2-ol (23.5 g, 264 mmol) in DMF (50 mL). The reaction mixture was stirred overnight at room temperature, then water (500 mL) was added and stirring was continued for 30 minutes. A solid was isolated by filtration,

washed with water, and dried to yield 60.9 g of 2-methyl-1-[(3-nitroquinolin-4-yl)amino]propan-2-ol, which was used without further purification.

Part B

A mixture of 2-methyl-1-[(3-nitroquinolin-4-yl)amino]propan-2-ol (60.9 g, 233 mmol), 5% platinum on carbon (6.1 g), and ethanol (500 mL) was hydrogenated on a Parr apparatus at 30 psi (2.1 x 10^5 Pa) for 3 hours. The mixture was filtered through CELITE filter agent, which was subsequently rinsed with methanol and dichloromethane. The filtrate was concentrated under reduced pressure to yield an oil that was concentrated twice from toluene to afford 56.6 g of a brown oil that was used directly in the next step.

Part C

Triethylamine (49.0 mL, 350 mmol) was added to a stirred suspension of the material from Part B in dichloromethane (450 mL). A solution of chloroacetyl chloride (21.0 mL, 257 mmol) in dichloromethane (50 mL) was added dropwise over 45 minutes. The reaction mixture was stirred for approximately 3 days at room temperature. The solution was concentrated under reduced pressure. The residue was partitioned between ethyl acetate (500 mL) and 1:1 saturated aqueous sodium bicarbonate/water (500 mL). The aqueous layer was extracted with ethyl acetate (3 x 250 mL) and chloroform (250 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The resulting pale brown solid was crystallized from dichloromethane (80 mL) to afford 25.7 g of 1-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol as pale yellow crystals. The mother liquor was concentrated and crystallized from dichloromethane (40 mL) to yield an additional 3.56 g of product. The mother liquor was concentrated under reduced pressure and the resulting residue was purified by chromatography using a HORIZON HPFC system (silica gel, gradient elution with 3-13% methanol in ethyl acetate) to afford 15.5 g of 1-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol.

Part D

mCPBA (77% pure, 36.5 g, 163 mmol) was added over 10 minutes to a stirred suspension of 1-[2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol (23.6 g, 81.4 mmol) in chloroform (500 mL). The resulting solution was stirred at room temperature for 1.5 hours. Concentrated ammonium hydroxide (200 mL) was added. After 5 minutes, *p*-toluenesulfonyl chloride (18.6 g, 97.7 mmol) was added in portions. The mixture was stirred at room temperature for 2.3 hours, then was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 100 mL, then 3 x 200 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to yield a foam. The crude product was purified in portions by chromatography on a HORIZON HPFC system (silica gel, elution with 5% methanol in chloroform followed by gradient elution with 5-15% methanol in chloroform) to yield 9.42 g of 1-[4-amino-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol as a pale yellow solid.

Part E

A solution of 1-[4-amino-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol (1.00 g, 3.28 mmol) in DMF (3.0 mL) was added to a solution of *N*-hydroxyphthalimide (642 mg, 3.94 mmol) and triethylamine (0.915 mL, 6.56 mmol) in DMF (3.0 mL). The flask containing the solution of 1-[4-amino-2-(chloromethyl)-1*H*-imidazo[4,5-*c*]quinolin-1-yl]-2-methylpropan-2-ol was rinsed with DMF (3.0 mL), which was added to the reaction solution. The solution was stirred at room temperature for 3 hours and a solid formed. The solid was isolated by filtration, washed with dichloromethane, and dried. The off-white solid was dissolved in hot DMF (20 mL). Acetonitrile (50 mL) was added to the solution, which was then placed in a freezer. Crystals formed and were isolated by filtration, washed with acetonitrile, and dried to provide 288 mg of 2-{[4-amino-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}-1*H*-isoindole-1,3(2*H*)-dione as orange crystals, mp 270-272 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.36 (d, J = 8.1 Hz, 1H), 7.85 (s, 4H), 7.60 (dd, J = 8.3, 1.3 Hz, 1H), 7.44 (ddd, J = 8.1, 7.0, 1.1 Hz, 1H), 7.24 (ddd, J = 8.1, 7.2, 1.3 Hz, 1H), 6.57 (br s, 2H), 5.67 (br s, 2H), 4.97 (s, 1H), 4.96 (br s, 2H), 1.24 (br s, 6H);

MS (APCI) *m/z* 432.0 $(M + H)^+$;

Anal. calcd for $C_{23}H_{21}N_5O_4$: C, 64.03; H, 4.91; N, 16.23. Found: C, 63.65; H, 4.65; N, 16.50.

Part F

Hydrazine (20 mL) was added to a stirred suspension of 2-{[4-amino-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}-1*H*-isoindole-1,3(2*H*)-dione (14.0 g, 32.4 mmol) in ethanol (100 mL). The mixture was stirred at room temperature and after 5 minutes a solution formed. After 1 hour, a solid began to form and additional ethanol (100 mL) was added. After 4.5 hours, the solid was isolated by filtration, washed with dichloromethane, and dried to yield 9.30 g of 1-{4-amino-2-[(aminooxy)methyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}-2-methylpropan-2-ol as a yellow solid, some of which was used without further purification in the next step. Two batches of the product (6.63 g and 1.00 g) were purified by chromatography using a HORIZON HPFC system (silica gel, gradient elution with 5-15% of 2 M NH_3 in methanol/chloroform) to provide 4.45 g and 650 mg of 1-{4-amino-2-[(aminooxy)methyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}-2-methylpropan-2-ol as a yellow solid, respectively. Some of the chromatographed product (650 mg) was crystallized from acetonitrile to yield 377 mg of 1-{4-amino-2-[(aminooxy)methyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}-2-methylpropan-2-ol as pale yellow crystals, mp 178-179 °C.

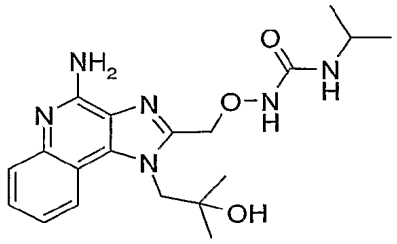
^{1}H NMR (300 MHz, DMSO-d_6) δ 8.28 (d, J = 8.1 Hz, 1H), 7.60 (dd, J = 8.3, 0.9 Hz, 1H), 7.40 (m, 1H), 7.21 (m, 1H), 6.58 (br s, 2H), 6.24 (br s, 2H), 5.02 (br s, 2H), 4.85, (s, 1H) 4.71 (br s, 2H), 1.17 (br s, 6H);

MS (APCI) *m/z* 302.2 $(M + H)^+$;

Anal. calcd for $C_{15}H_{19}N_5O_2$: C, 59.79; H, 6.36; N, 23.24. Found: C, 59.93; H, 6.38; N, 23.40.

Example 101

N-{[4-Amino-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}-*N'*-isopropylurea



Isopropyl isocyanate (0.234 mL, 2.39 mmol) was added to a stirred solution of 1-{4-amino-2-[(aminooxy)methyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}-2-methylpropan-2-ol (prepared as described in Example 100, 600 mg, 1.99 mmol) in DMF (5 mL). After 5 minutes, a solid formed. The mixture was stirred for 1 hour and 45 minutes, then additional isopropyl isocyanate (0.234 mL) and DMF (2 mL) was added. The mixture was stirred at room temperature for 45 minutes. Water (40 mL) was added and a solid was isolated by filtration. The solid was washed with water and dried under vacuum to provide 272 mg of *N*-{[4-amino-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}-*N'*-isopropylurea as a white solid. The filtrate was allowed to stand overnight at room temperature and crystals formed. The crystals were isolated by filtration, washed with acetontrile, and dried in a vacuum oven at 60 °C to afford additional 38 mg of *N*-{[4-amino-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}-*N'*-isopropylurea, as yellow crystals, mp 231-233 °C.

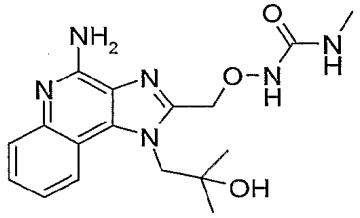
^{1}H NMR (300 MHz, DMSO-d_6) δ 9.16 (s, 1H), 8.27 (d, J = 7.7 Hz, 1H), 7.60 (dd, J = 8.4, 1.3 Hz, 1H), 7.41 (m, 1H), 7.22 (ddd, J = 8.3, 7.3, 1.4 Hz, 1H), 6.62 (br s, 2H), 6.46 (d, J = 8.1 Hz, 1H), 5.17 (br s, 2H), 4.93 (s, 1H), 4.70 (br s, 2H), 3.67 (m, 1H), 1.17 (br s, 6H), 0.97 (d, J = 6.7 Hz, 6H);

MS (APCI) *m/z* 387.1 $(M + H)^+$;

Anal. calcd for $C_{19}H_{26}N_6O_3$: C, 59.05; H, 6.78; N, 21.75. Found: C, 58.78; H, 6.86; N, 21.64.

Example 102

N-{[4-Amino-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}-*N'*-methylurea



Methyl isocyanate (0.148 mL, 2.39 mmol) was added to a stirred solution of 1-{4-amino-2-[(aminooxy)methyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}-2-methylpropan-2-ol (prepared as described in Example 100, 600 mg, 1.99 mmol) in DMF (5 mL). A solid formed immediately. The mixture was stirred for 2 hours at room temperature, then was heated to form a solution to which acetonitrile (10 mL) was added. Crystals formed that were isolated by filtration and purified by chromatography using a HORIZON HPFC (silica gel, gradient elution with 5-20% 2 M NH_3 in methanol/chloroform). The appropriate fractions were combined and concentrated to a solid that was dried in a vacuum oven overnight to afford *N*-{[4-amino-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}-*N'*-methylurea as white crystals, mp 206-207 °C.

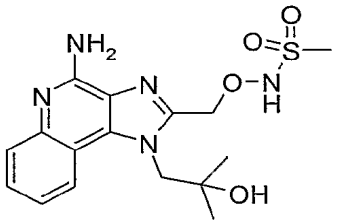
^{1}H NMR (300 MHz, DMSO-d_6) δ 9.17 (s, 1H), 8.26 (d, J = 8.1 Hz, 1H), 7.60 (dd, J = 8.3, 1.3 Hz, 1H), 7.41 (ddd, J = 8.1, 7.0, 1.1 Hz, 1H), 7.21 (ddd, J = 8.3, 6.9, 1.3 Hz, 1H), 7.04 (q, J = 4.7Hz, 1H), 6.60 (br s, 2H), 5.17 (br s, 2H), 4.92 (s, 1H), 4.67 (br s, 2H), 2.60 (d, J = 4.7 Hz, 3H), 1.17 (br s, 6H);

MS (APCI) *m/z* 359.0 $(M + H)^+$;

Anal. calcd for $C_{17}H_{22}N_6O_3$: C, 56.97; H, 6.19; N, 23.45. Found: C, 56.80; H, 6.27; N, 23.45.

Example 103

N-{[4-Amino-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}methanesulfonamide



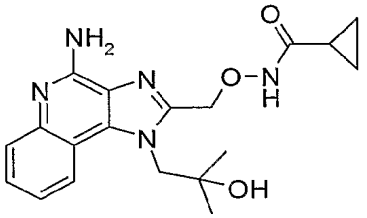
Triethylamine (0.634 mL, 4.55 mmol) and methanesulfonyl chloride (0.211 mL, 2.73 mmol) were added to a solution of 1-{4-amino-2-[(aminooxy)methyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}-2-methylpropan-2-ol (prepared as described in Example 100, 685 mg, 2.27 mmol) in DMF (5 mL). A solid formed immediately. The mixture was stirred for 3.5 hours at room temperature, then additional triethylamine (0.634 mL) and methanesulfonyl chloride (0.211 mL) were added. The reaction mixture was stirred for an additional 1.5 hours, then was partitioned between water (20 mL) and dichloromethane (30 mL). The aqueous layer was extracted with dichloromethane (2 x 30 mL). The organic layers were combined and allowed to stand overnight at room temperature. Crystals formed and were isolated by filtration to provide 40 mg of *N*-{[4-amino-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}methanesulfonamide. Additional crystals were isolated from the mother liquor after a seed crystal was added. The two crops were combined and dried in a vacuum oven to provide 160 mg of *N*-{[4-amino-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}methanesulfonamide as pale yellow crystals, mp 232-234 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 10.1 (br s, 1H), 8.30 (d, J = 8.4 Hz, 1H), 7.60 (dd, J = 8.3, 1.3 Hz, 1H), 7.41 (ddd, J = 8.1, 7.0, 1.1 Hz, 1H), 7.21 (ddd, J = 8.1, 7.2, 1.3 Hz, 1H), 6.62 (br s, 2H), 5.35 (br s, 2H), 4.91 (s, 1H), 4.72 (br s, 2H), 3.01 (s, 3H), 1.17 (br s, 6H); MS (APCI) *m/z* 380.1 $(M + H)^+$;

Anal. calcd for $C_{16}H_{21}N_5O_4S$: C, 50.65; H, 5.58; N, 18.46. Found: C, 50.69; H, 5.89; N, 18.76.

Example 104

N-{[4-Amino-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}cyclopropanecarboxamide



Triethylamine (0.634 mL, 4.55 mmol) and cyclopropanecarbonyl chloride (0.248 mL, 2.73 mmol) were added to a solution of 1-{4-amino-2-[(aminooxy)methyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}-2-methylpropan-2-ol (prepared as described in Example 100, 685 mg, 2.27 mmol) in DMF (5 mL). The cloudy mixture was stirred for 2 hours at room temperature, then was partitioned between water (20 mL) and dichloromethane (30 mL). The aqueous layer was extracted with dichloromethane (2 x 30 mL). The organic layers were combined and allowed to stand overnight at room temperature. Crystals formed and were isolated by filtration, washed with dichloromethane and acetonitrile, and dried in a vacuum oven to provide 442 mg of *N*-{[4-Amino-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}cyclopropanecarboxamide as a hydrate, white crystals, mp 209-210 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.3 (br s, 1H), 8.30 (d, J = 8.1 Hz, 1H), 7.60 (dd, J = 8.4, 1.3 Hz, 1H), 7.41 (m, 1H), 7.22 (m, 1H), 6.62 (br s, 2H), 5.27 (br s, 2H), 4.86 (s, 1H), 4.81 (br s, 2H), 1.38 (m, 1H), 1.18 (br s, 6H), 0.70 (d, J = 6.4 Hz, 4H);

MS (APCI) *m/z* 370.0 $(M + H)^+$;

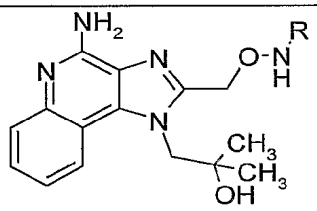
Anal. calcd for $C_{19}H_{23}N_5O_3 \cdot H_2O$: C, 58.90; H, 6.50; N, 18.08. Found: C, 59.08; H, 6.87; N, 18.48.

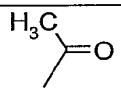
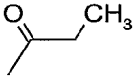
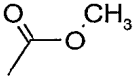
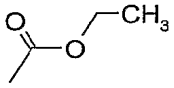
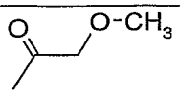
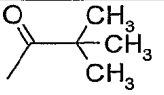
Examples 105-122

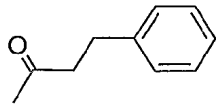
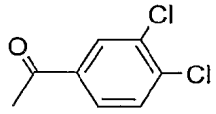
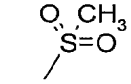
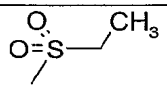
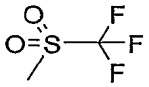
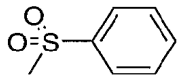
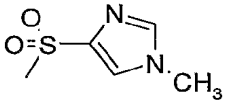
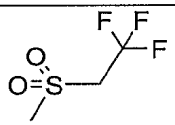
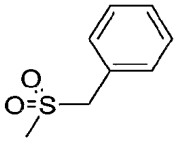
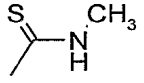
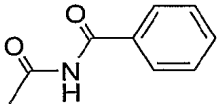
A reagent from the table below (1.1 equivalents, 0.10 mmol) was added to a test tube containing a solution of 1-{4-amino-2-[(aminooxy)methyl]-1*H*-imidazo[4,5-*c*]quinolin-1-yl}-2-methylpropan-2-ol (prepared as described in Example 100, 29 mg, 0.09 mmol) and triethylamine (26 μL, 0.20 mmol) in DMF (1 mL). The test tubes were capped and placed on a shaker at ambient temperature overnight (approximately 18 hours). The

solvent was removed from the test tubes by vacuum centrifugation. The compounds were purified by preparative high performance liquid chromatography (prep HPLC) using a Waters FractionLynx automated purification system. The prep HPLC fractions were analyzed using a Waters LC/TOF-MS, and the appropriate fractions were centrifuge evaporated to provide the trifluoroacetate salt of the desired compound. Reversed phase preparative liquid chromatography was performed with non-linear gradient elution from 5-95% B where A is 0.05% trifluoroacetic acid/water and B is 0.05% trifluoroacetic acid/acetonitrile. Fractions were collected by mass-selective triggering. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

Examples 105-122

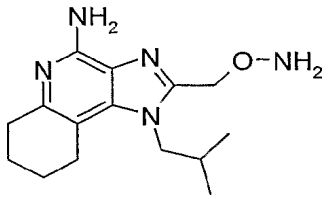


Example	Reagent	R	Measured Mass (M+H)
105	None		302.1606
106	Acetyl chloride		344.1752
107	Propionyl chloride		358.1905
108	Methyl chloroformate		360.1704
109	Ethyl chloroformate		374.1866
110	Methoxyacetyl chloride		374.1858
111	Pivaloyl chloride		386.2218

112	Hydrocinnamoyl chloride		434.2190
113	3,4-Dichlorobenzoyl chloride		474.1079
114	Methanesulfonyl chloride		380.1404
115	Ethanesulfonyl chloride		394.1535
116	Trifluoromethanesulfonyl chloride		442.1525
117	Benzenesulfonyl chloride		442.1527
118	1-Methylimidazole-4-sulfonyl chloride		446.1650
119	2,2,2-Trifluoroethanesulfonyl chloride		448.1269
120	*alpha*-Toluenesulfonyl chloride		456.1681
121	Methyl isothiocyanate		375.1618
122	Benzoyl isocyanate		449.1935

Example 123

2-[(Aminooxy)methyl]-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine



Part A

A mixture of [4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol (15.2 g, 56.2 mmol, U.S. Pat. No. 5,389,640 Example 9), platinum(IV) oxide (7.6 g), and trifluoroacetic acid (75 mL) was hydrogenated at 50 psi (3.5×10^5 Pa) of hydrogen on a Parr apparatus for 2 days. The mixture was diluted with dichloromethane and filtered through CELITE filter agent, which was rinsed afterwards with dichloromethane and methanol. The filtrate was concentrated under reduced pressure and the residue was partitioned between dichloromethane (250 mL) and 1:1 saturated aqueous sodium bicarbonate/water (250 mL). Some solid formed that was isolated by filtration. The aqueous layer was extracted with dichloromethane (2 x 200 mL). The solid was dissolved in methanol and the resulting solution was combined with the organic layers, concentrated under reduced pressure, and purified by chromatography using a HORIZON HPFC system (silica gel, elution with 10% 1 M NH_3 in methanol/dichloromethane) to afford 4.98 g of [4-amino-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol as a grey solid.

Part B

Thionyl chloride (2.65 mL, 36.2 mmol) was added dropwise to a stirred suspension of [4-amino-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methanol (4.97 g, 18.1 mmol) in 1,2-dichloroethane (200 mL). The suspension dissolved, then a precipitate formed after 5 minutes. The reaction mixture was stirred at room temperature for 6 hours, then was concentrated under reduced pressure to yield crude 2-(chloromethyl)-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine hydrochloride, all of which was used in the next step.

Part C

A solution of *N*-hydroxyphthalimide (3.54 g, 21.7 mmol) and triethylamine (7.6 mL, 54.3 mmol) in DMF (25 mL) was added to a suspension of the material from Part B in DMF (25 mL) at room temperature. The reaction mixture was stirred at room temperature overnight, then was concentrated under reduced pressure and used without purification in the next step.

Part D

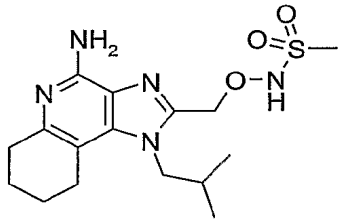
Hydrazine hydrate (8.8 mL, 181 mmol) was added to a solution of the material from Part C in ethanol (180 mL). The reaction mixture was stirred overnight and a solid formed that was removed by filtration. The filtrate was concentrated under reduced pressure, then was purified by chromatography using a HORIZON HPFC system (silica gel, gradient elution with 5-10% 1 M NH_3 in methanol/dichloromethane) to afford 4.52 g of 2-[(aminooxy)methyl]-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a pale yellow foam.

MS (APCI) *m/z* 290.2 $(M + H)^+$;

^{1}H NMR (300 MHz, DMSO-d_6) δ 6.26 (br s, 2H), 5.85 (br s, 2H), 4.77 (s, 2H), 4.14 (d, J = 7.6 Hz, 2H), 2.91 (m, 2H), 2.67 (m, 2H), 2.00 (m, 1H), 1.76 (m, 4H), 0.84 (d, J = 6.7 Hz, 6H).

Example 124

N-{[4-Amino-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}methanesulfonamide hydrochloride



A solution of methanesulfonyl chloride (0.253 mL, 3.27 mmol) in dichloromethane (10 mL) was added dropwise to a stirred solution of 2-[(aminooxy)methyl]-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine (prepared as

described in Example 123, 860 mg, 2.97 mmol) and triethylamine (1.24 mL, 8.92 mmol) in dichloromethane (20 mL) at 0 °C. After 1 hour, additional methanesulfonyl chloride (0.125 mL in dichloromethane (5 mL)) and triethylamine (0.5 mL) were added. The reaction mixture was stirred for an additional 30 minutes, then was concentrated under reduced pressure to afford a yellow foam. The foam was purified by chromatography using a HORIZON HPFC system (silica gel, gradient elution with 5-15% 1 M NH_3 in methanol/dichloromethane) followed by crystallization from methanol/acetonitrile. The crystals were isolated by filtration, washed with acetonitrile, and dried in a vacuum oven to yield 160 mg of *N*-{[4-amino-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}methanesulfonamide hydrochloride as a white crystals, mp 211-213 °C.

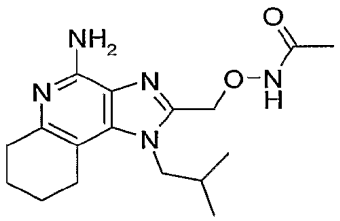
^{1}H NMR (300 MHz, DMSO-d_6) δ 13.6 (br s, 1H), 10.4 (s, 1H), 8.26 (br s, 2H), 5.18 (s, 2H), 4.28 (d, J = 7.7 Hz, 2H), 3.04 (s, 3H), 2.94 (br s, 2H), 2.79 (br s, 2H), 2.06 (m, 1H), 1.80 (br s, 4H), 0.88 (d, J = 6.6 Hz, 6H);

MS (APCI) *m/z* 368.2 $(M + H)^+$;

Anal. calcd for $C_{16}H_{25}N_5O_3S$•HCl: C, 47.58; H, 6.49; N, 17.34. Found: C, 47.68; H, 6.51; N, 17.38.

Example 125

N-{[4-Amino-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}acetamide



A solution of acetyl chloride (0.232 mL, 3.27 mmol) in dichloromethane (10 mL) was added dropwise to a stirred solution of 2-[(aminooxy)methyl]-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine (prepared as described in Example 123, 860 mg, 2.97 mmol) and triethylamine (1.24 mL, 8.92 mmol) in dichloromethane (20 mL) at 0 °C. After 1 hour, additional acetyl chloride (0.232 mL) in dichloromethane (10 mL) and triethylamine (1.0 mL) were added. The reaction mixture was stirred for an

additional 30 minutes, then was concentrated under reduced pressure. The crude product was purified by chromatography using a HORIZON HPFC system (silica gel, gradient elution with 5-15% 1 M NH_3 in methanol/dichloromethane) followed by crystallization from acetonitrile. The crystals were isolated by filtration, washed with acetonitrile, and dried in a vacuum oven to yield 257 mg of *N*-{[4-amino-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}acetamide as pale yellow crystals, mp 187-188 °C.

^{1}H NMR (300 MHz, DMSO-d_6) δ 11.1 (br s, 1H), 5.91 (br s, 2H), 4.99 (br s, 2H), 4.32 (d, J = 7.2 Hz, 2H), 2.93 (br s, 2H), 2.67 (br s, 2H), 2.02 (m, 1H), 1.76 (m, 7H), 0.86 (d, J = 6.7 Hz, 6H);

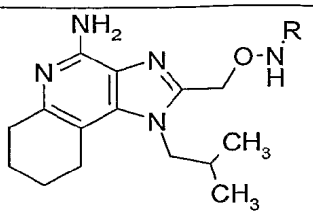
MS (APCI) *m/z* 332.2 $(M + H)^+$;

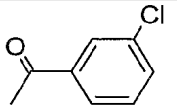
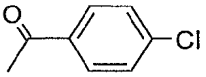
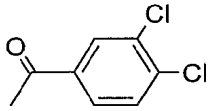
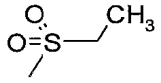
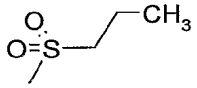
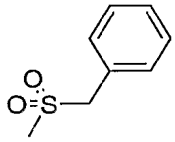
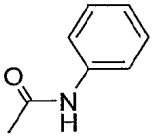
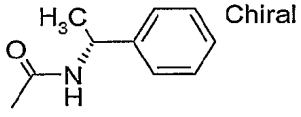
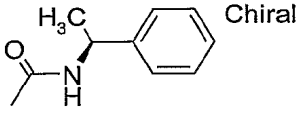
Anal. calcd for $C_{17}H_{25}N_5O_2$: C, 61.61; H, 7.60; N, 21.13. Found: C, 61.52; H, 7.73; N, 21.38.

Examples 126-135

A reagent from the table below (1.1 equivalents, 0.11 mmol) was added to a test tube containing a solution of 2-[(aminooxy)methyl]-1-(2-methylpropyl)-6,7,8,9-tetrahydro-1*H*-imidazo[4,5-*c*]quinolin-4-amine (prepared as described in Example 123, 29 mg, 0.10 mmol) and *N,N*-diisopropylethylamine (36 μL, 0.20 mmol) in chloroform (1 mL). The test tubes were capped and placed on a shaker at ambient temperature for 4 hours. Water (two drops) was added to each test tube and the volatiles were removed from the test tubes by vacuum centrifugation. The compounds were purified as described in Examples 105-122. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

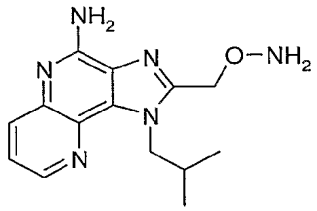
Examples 126-135



Example	Reagent	R	Measured Mass (M+H)
126	None		290.1982
127	3-Chlorobenzoyl chloride		428.1879
128	4-Chlorobenzoyl chloride		428.1862
129	3,4-Dichlorobenzoyl chloride		462.1498
130	Ethanesulfonyl chloride		382.1924
131	1-Propanesulfonyl chloride		396.2091
132	*alpha*-Toluenesulfonyl chloride		444.2097
133	Phenyl isocyanate		409.2379
134	(R)-(+)- *alpha* - Methylbenzyl isocyanate	 Chiral	437.2697
135	(S)-(-)- *alpha* - Methylbenzyl isocyanate	 Chiral	437.2682

Example 136

2-[(Aminooxy)methyl]-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine



Part A

Isobutylamine (15.6 mL, 157 mmol) was added dropwise to a 5 °C solution of 4-chloro-3-nitro[1,5]naphthyridine (15.0 g, 71.6 mmol) in dichloromethane (300 mL). The reaction was allowed to stir at room temperature for 4 hours, then was concentrated under reduced pressure to afford a residue that was treated with water (300 mL). The mixture was stirred for 30 minutes, then a solid was isolated by filtration, rinsed with water (100 mL), and dried in a vacuum oven at 50 °C overnight to afford 17.25 g of *N*-(2-methylpropyl)-3-nitro[1,5]naphthyridin-4-amine as a yellow solid.

Part B

The general method described in Part B of Example 92 was used to convert *N*-(2-methylpropyl)-3-nitro[1,5]naphthyridin-4-amine (17.25 g, 70.0 mmol) into N^4-(2-methylpropyl)[1,5]naphthyridine-3,4-diamine, which was isolated as a thick, yellow oil and used directly in the next step without purification.

Part C

The general method described in Part C of Example 92 was used to convert N^4-(2-methylpropyl)[1,5]naphthyridine-3,4-diamine (from Part B) into 2-chloro-*N*-{4-[(2-methylpropyl)amino][1,5]naphthyridin-3-yl}acetamide hydrochloride, which was isolated as a pale yellow solid that was used directly in the next step without purification.

Part D

To a solution of 2-chloro-*N*-{4-[(2-methylpropyl)amino][1,5]naphthyridin-3-yl}acetamide hydrochloride (from Part C, approximately 70 mmol) in 3:1 ethanol/water (280 mL) was added 6 M aqueous potassium carbonate (17.5 mL). The reaction mixture

was stirred at room temperature over the weekend. The volatiles were removed under reduced pressure and the residue was partitioned between dichloromethane (200 mL) and brine (100 mL). The aqueous layer was extracted with dichloromethane (2 x 50 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to afford 19.5 g of 2-(chloromethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine, which contained a small amount of dichloromethane and was used without further purification in the next step.

Part E

mCPBA (70% pure, 9.85 g, 40.0 mmol) was added to a solution of 2-(chloromethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridine (5.49 g, 20.0 mmol) in chloroform (80 mL). The reaction mixture was allowed to stir for 1.5 hours, then was diluted with dichloromethane (150 mL) and washed with saturated aqueous sodium bicarbonate (2 x 75 mL). The aqueous layers were combined and back-extracted with dichloromethane (2 x 30 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated to afford a yellow semi-solid that was used immediately without purification in the next step.

Part F

The material from Part E was dissolved in methanol (70 mL) and the solution was cooled to 0 °C. Concentrated ammonium hydroxide (6.7 mL) was added, followed by dropwise addition of benzenesulfonyl chloride (5.25 mL, 42.0 mmol). The reaction mixture was stirred at 0 °C for 1 hour. The volatiles were removed under reduced pressure and the residue was partitioned between dichloromethane (150 mL) and saturated aqueous sodium bicarbonate (75 mL). The aqueous layer was extracted with dichloromethane (50 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated. The crude product was purified by chromatography using a HORIZON HPFC system (silica gel, gradient elution with 0-25 % CMA in chloroform) to afford 4.14 g of approximately 85% pure 2-(chloromethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine, which was used in the next step without further purification.

Part G

The general method described in Part H of Example 92 was used to convert the material from Part F (85% pure, 4.14 g, 14.3 mmol) into 2.81 g of 2-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methoxy}-1*H*-isoindole-1,3(2*H*)-dione.

Part H

Anhydrous hydrazine (0.640 mL, 20.2 mmol) was added to a suspension of 2-{[4-amino-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-2-yl]methoxy}-1*H*-isoindole-1,3(2*H*)-dione (2.81 g, 6.75 mmol) in ethanol (40 mL). Gradually, a solution formed from which a solid began to precipitate. The reaction mixture was stirred overnight at room temperature, then was concentrated under reduced pressure. The residue was triturated with 1 M aqueous hydrochloric acid (50 mL). The mixture was sonicated and the solid was isolated by filtration. The filtrate was adjusted to pH 8 with solid sodium carbonate and extracted with dichloromethane (3 x 25 mL). The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated to afford a yellow solid. The solid was triturated with methanol to afford 0.863 g of 2-[(aminooxy)methyl]-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine as a white powder.

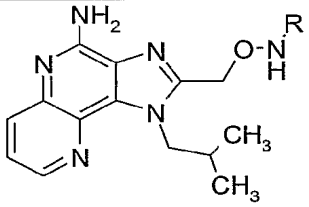
^{1}H NMR (500 MHz, DMSO-d6) δ 8.52 (dd, J = 4.3, 1.6 Hz, 1H), 7.91 (dd, J = 8.4, 1.6 Hz, 1H), 7.44 (dd, J = 8.4, 4.3 Hz, 1H), 6.88 (br s, 2H), 6.35 (br s, 2H), 4.90 (s, 2H), 4.73 (d, J = 7.5 Hz, 2H), 2.37 (septet, J = 7.0 Hz, 1H), 0.89 (d, J = 6.7 Hz, 6H);
MS (APCI) *m/z* 287 $(M+1)^+$.

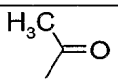
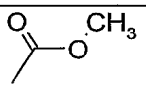
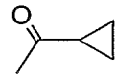
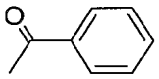
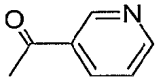
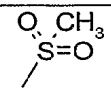
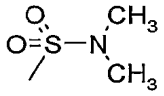
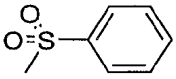
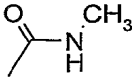
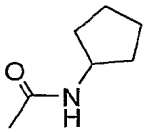
Examples 136-148

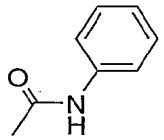
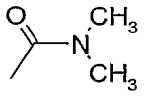
A reagent from the table below (1.1 equivalents, 0.11 mmol) was added to a test tube containing a solution of 2-[(aminooxy)methyl]-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*][1,5]naphthyridin-4-amine (prepared as described in Example 136, 29 mg, 0.10 mmol) and *N,N*-diisopropylethylamine (35 µL, 0.20 mmol) in chloroform (1 mL). The test tubes were capped and placed on a shaker at ambient temperature for 4 hours. The solvent was removed from the test tubes by vacuum centrifugation. The compounds were purified as

described in Examples 105-122. The table below shows the reagent used for each example, the structure of the resulting compound, and the observed accurate mass for the isolated trifluoroacetate salt.

Examples 136-148



Example	Reagent	R	Measured Mass (M+H)
136	None		287.1622
137	Acetyl chloride		329.1753
138	Methyl chloroformate		345.1709
139	Cyclopropanecarbonyl chloride		355.1909
140	Benzoyl chloride		391.1922
141	Nicotinoyl chloride hydrochloride		392.1858
142	Methanesulfonyl chloride		365.1428
143	Dimethylsulfamoyl chloride		394.1627
144	Benzenesulfonyl chloride		427.1565
145	Methyl isocyanate		344.1871
146	Cyclopropyl isocyanate		398.2327

147	Phenyl isocyanate		406.1998
148	*N,N*-Dimethylcarbamoyl chloride		358.2017

Examples 149-167

Part A

A mixture of triethyl orthoformate (154 g, 1.04 mol) and Meldrum's acid (142 g, 0.983 mol) was heated to 55°C for 4 hours. After cooling to 50 °C, a solution of 3-bromoaniline (162.6 g, 0.945 mol) in ethanol (300 mL) was added such that the temperature of the reaction was maintained between 50-55 °C. After half of the 3-bromoaniline had been added, stirring became difficult due to the formation of solids, so more ethanol (1 L) was added to facilitate stirring. Upon complete addition, the reaction was cooled to room temperature, and the solids were collected by filtration. The filter cake was washed with ice cold ethanol until the washings were nearly colorless, and the product was dried at 65 °C under vacuum to afford 287 g of 5-[(3-bromophenylimino)methyl]-2,2-dimethyl-1,3-dioxane-4,6-dione as an off-white solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 11.19 (brd, J = 12.8 Hz, 1H), 8.60 (d, J = 14.0 Hz, 1H), 7.44-7.38 (m, 2H), 7.30 (t, J = 8.0 Hz, 1H), 7.18 (ddd, J = 8.0, 2.2, 0.9 Hz, 1H), 1.75 (s, 6H).

Part B

7-Bromoquinolin-4-ol was prepared in accordance with the literature procedure (D. Dibyendu et al., *J. Med. Chem.*, *41*, 4918-4926 (1998)) or by thermolysis of 5-[(3-bromophenylimino)methyl]-2,2-dimethyl-1,3-dioxane-4,6-dione in DOWTHERM A heat transfer fluid and had the following spectral properties:

^{1}H NMR (300 MHz, d_6-DMSO) δ 11.70 (brs, 1H), 8.00 (d, J = 8.7 Hz, 1H), 7.92 (d, J = 7.5 Hz, 1H), 7.74 (d, J = 1.9 Hz, 1H), 7.44 (dd, J = 8.7, 1.9 Hz, 1H), 6.05 (d, J = 7.5 Hz, 1H).

Part C

A stirred suspension of 7-bromoquinolin-4-ol (162 g, 0.723 mol) in propionic acid (1500 mL) was brought to 110 °C. Nitric acid (85 g of 70%) was added dropwise over 1 hour such that the temperature was maintained between 110-115 °C. After half of the nitric acid had been added, stirring became difficult due to the formation of solids and an additional 200 mL of propionic acid was added. Upon complete addition, the reaction was stirred for 1 hour at 110°C, cooled to room temperature, and the solid was collected by filtration. The filter cake was washed with ice cold ethanol until the washings were nearly colorless (800 mL), and the product was dried at 60 °C under vacuum to afford 152 g of 7-bromo-3-nitro-quinolin-4-ol as a pale yellow solid.

^{1}H NMR (300 MHz, d_6-DMSO) δ 13.0 (brs, 1H), 9.22 (s, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 1.6 Hz, 1H), 7.66 (dd, J = 8.7, 1.9 Hz, 1H).

Part D

7-Bromo-3-nitroquinolin-4-ol (42 g, 156 mmol) was suspended in $POCl_3$ (130 mL) and brought to 102 °C under an atmosphere of N_2. After 45 min, all of the solids had dissolved, so the reaction was cooled to room temperature. The resulting solids were collected by filtration, washed with H_2O, and then partitioned with CH_2Cl_2 (3 L) and 2M Na_2CO_3 (500 mL). The organic layer was separated, washed with H_2O (1x), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford 33.7 g of 7-bromo-4-chloro-3-nitroquinoline as a beige solid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.26 (s, 1H), 8.41 (d, J = 1.8 Hz, 1H), 8.30 (d, J = 9.0 Hz, 1H), 7.90 (dd, J = 8.9, 2.1 Hz, 1H).

Part E

To a suspension of 7-bromo-4-chloro-3-nitroquinoline (25.0 g, 87.0 mmol) in DMF (70 mL) was added triethylamine (18.2 mL, 130 mmol). A solution of *iso*-butylamine (9.50 mL, 95.7 mmol) in DMF (20 mL) was added dropwise. The viscous reaction mixture was stirred overnight at ambient temperature. Water (200 mL) was added and the mixture was stirred for 1 hour. A solid was isolated by filtration, washed with water, and dried in a vacuum oven overnight to yield 26.1 g of 7-bromo-*N*-(2-methylpropyl)-3-nitroquinolin-4-amine as a yellow powder.

Part F

A mixture of 7-bromo-*N*-(2-methylpropyl)-3-nitroquinolin-4-amine (25.1 g, 77.4 mmol) and 5% platinum on carbon (2.5 g), dichloroethane (160 mL), and ethanol (80 mL) was hydrogenated on a Parr apparatus at 30 psi (2.1 x 10^5 Pa) for 2 hours. The mixture was filtered through CELITE filter agent and the filtrate was concentrated under reduced pressure to yield 23.1 g of a brown oil.

Part G

To a stirred solution of the material from Part F (23.1 g) and triethylamine (16.4 mL, 118 mmol) in dichloromethane (300 mL) was added dropwise chloroacetyl chloride (6.9 mL, 86.3 mmol). The reaction mixture was allowed to stir at room temperature for 7 days, then was concentrated under reduced pressure. The resulting brown foam was partitioned between ethyl acetate (400 mL) and 1:1 saturated aqueous sodium bicarbonate/water (400 mL). The water layer was extracted with dichloromethane (2 x 200 mL). The organic layers were combined and concentrated under reduced pressure. The crude product was divided into three portions, which were purified by chromatography on a HORIZON HPFC system (silica gel, gradient elution with ethyl acetate in hexanes). The purified material was combined to yield 18.32 g of 7-bromo-2-(chloromethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline as a yellow solid.

Part H

To a solution of 7-bromo-2-(chloromethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinoline (13.9 g, 39.4 mmol) in chloroform (300 mL) at room temperature was added mCPBA (77% pure, 17.7 g, 78.8 mmol) over ten minutes. The reaction mixture was stirred at room temperature for 3 hours, then concentrated ammonium hydroxide (150 mL) was added, followed by *p*-toluenesulfonyl chloride (9.00 g, 47.3 mmol, added in portions over 10 minutes). The mixture was stirred at room temperature for 1 hour, then was transferred to a separatory funnel. The layers were separated and the aqueous layer was extracted with dichloromethane (2 x 100 mL). The organic layers were combined, dried over magnesium sulfate, filtered through CELITE filter agent, and concentrated under

reduced pressure. The crude product was purified by chromatography using a HORIZON HPFC system (silica gel, gradient elution with ethyl acetate in hexanes) to yield 7.69 g of 7-bromo-2-(chloromethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a yellow foam.

Part I

A solution of 7-bromo-2-(chloromethyl)-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (7.65 g, 20.8 mmol) in DMF (20 mL) was added dropwise via addition funnel to a solution of *N*-hydroxyphthalimide (4.07 g, 25.0 mmol) and triethylamine (4.3 mL, 31.2 mmol) in DMF (20 mL). The addition funnel was rinsed with DMF (20 mL) and the rinse was added to the reaction solution, which was stirred at room temperature. After 30 minutes, a precipitate formed. The viscous mixture was stirred at room temperature overnight, then diethyl ether (150 mL) was added. The solid was isolated by filtration, washed with diethyl ether, and dried under vacuum to provide 7.44 g of 2-{[4-amino-7-bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methoxy}-1*H*-isoindole-1,3(2*H*)-dione, which contained some triethylamine hydrochloride. The filtrate was concentrated to yield 8.5 g of a brown oil, which was found to contain product and was combined with the material from above and used in the next step.

Part J

Anhydrous hydrazine (20 mL) was added to a stirred suspension of the material from Part I (approximately 20.8 mmol) in ethanol (150 mL) at room temperature. The mixture became homogeneous after 2 minutes. After 30 minutes, a precipitate had formed. The mixture was stirred for another 1.5 hours, then was filtered through CELITE filter agent. The filtrate was concentrated under reduced pressure to afford crude 2-[(aminooxy)methyl]-7-bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine as a brown solid, which was used in the next step without purification.

Part K

The material from Part J was dissolved in methanol (150 mL) and acetone (50 mL). The solution was stirred at room temperature for 3 hours, then was concentrated under

reduced pressure to yield a brown solid. Dichloromethane (100 mL) was added and the mixture was stirred for 30 minutes, then filtered. The filtrate was concentrated under reduced pressure and purified by chromatography three times on a HORIZON HPFC system (silica gel) to yield 4.11 g of acetone *O*-{[4-amino-7-bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}oxime as a pale orange solid.

Part L

3-Bromo-5-(*tert*-butyldimethylsilanyloxymethyl)pyridine was prepared according to the published procedure (Zhang, N. et al, *J. Med. Chem.*, *45*, 2832-2840 (2002)). Under a nitrogen atmosphere, a solution of 3-bromo-5-(*tert*-butyldimethylsilanyloxymethyl)pyridine (28.70 g, 94.94 mmol) and triisopropyl borate (26.3 mL, 114 mmol) in dry THF was cooled to -70 °C. *n*-Butyllithium (45.6 mL, 114 mmol) was added dropwise over a period of 1.5 hours. The reaction was stirred for an additional 30 minutes and then allowed to warm to -20 °C. Dilute aqueous ammonium chloride was added, and the mixture was allowed to warm to ambient temperature. The aqueous layer was separated and extracted with diethyl ether. The combined organic fractions were concentrated under reduced pressure, and methanol was added to the resulting oil. A solid formed, which was stirred with water for two days, isolated by filtration, and dried under reduced pressure to provide 18.19 g of 5-(*tert*-butyldimethylsilanyloxymethyl)pyridine-3-boronic acid as a white solid.

Part M

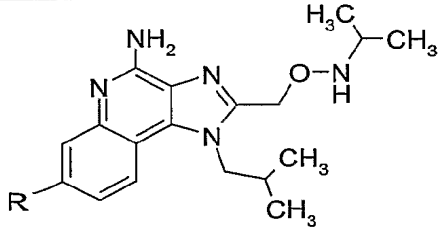
The compounds in the table below can be prepared according to the following method. A solution of acetone *O*-{[4-amino-7-bromo-1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-2-yl]methyl}oxime (prepared as described in Parts A-K above, 0.20 mmol) in 7:3 volume:volume (v:v) chloroform:methanol (2 mL) can be added to a test tube, and the solvent can be removed by vacuum centrifugation. The boronic acid (0.22 mmol) indicated in the table below and *n*-propanol (3.2 mL) can be sequentially added, and the test tube can be purged with nitrogen. The reaction mixture can be sonicated until a solution forms. Palladium (II) acetate (0.292 mL of a 0.018 M solution in toluene, 0.0053 mmol), 2M aqueous sodium carbonate solution (1.2 mL), deionized water

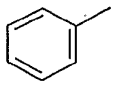
(225 μL), and a solution of 0.15 M triphenylphosphine in *n*-propanol (106 μL, 0.0159 mmol) can be added sequentially. The test tube can be purged with nitrogen, capped, and then heated to 80 °C overnight in a sand bath. For Example 158, the solvent can be removed by vacuum centrifugation, and glacial acetic acid (1 mL), tetrahydrofuran (1 mL), and deionized water (1 mL) can be added to the test tube. The reaction can be heated overnight at 60 °C. The solvent can be removed from the test tubes by vacuum centrifugation.

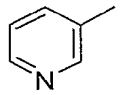
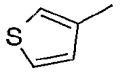
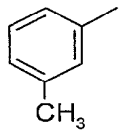
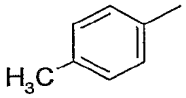
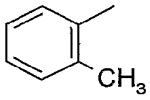
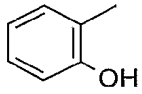
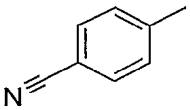
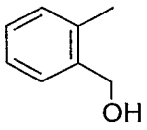
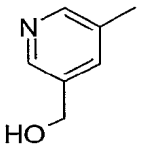
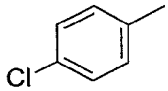
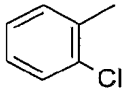
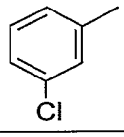
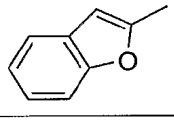
The contents of each test tube can be passed through a Waters Oasis Sample Extractions Cartridge MCX (6 cc) according to the following procedure. Hydrochloric acid (3 mL of 1 N) can be added to adjust each example to pH 5-7, and the resulting solution can be passed through the cartridge optionally using light nitrogen pressure. The cartridge can be washed with methanol (5 mL) optionally using light nitrogen pressure and transferred to a clean test tube. A solution of 1% ammonia in methanol (2 x 5 mL) can be then passed through the cartridge optionally using light nitrogen pressure, and the basic solution can be collected and concentrated.

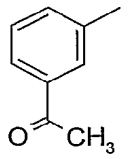
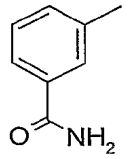
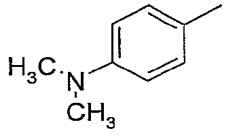
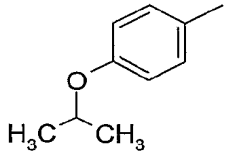
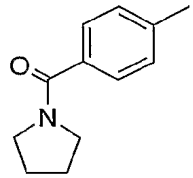
The residue in each test tube can be dissolved in methanol (1 mL) and glacial acetic acid (1 mL). To each solution can be added a solution of sodium cyanoborohydride in tetrahydrofuran (1 M, 300-500 μL, 0.3-0.5 mmol). The test tubes can be capped and placed on a shaker at ambient temperature overnight. The solvent can be removed from the test tubes by vacuum centrifugation. The compounds can be purified as described in Examples 105-122. The table below shows the boronic acid that can be used for each example and the structure of the resulting compound.

Examples 149-167



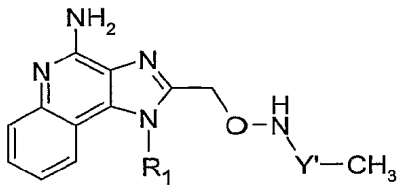
Example	Reagent	R
149	Phenylboronic acid	

150	Pyridine-3-boronic acid	
151	Thiophene-3-boronic acid	
152	3-Methylphenylboronic acid	
153	4-Methylphenylboronic acid	
154	*o*-Tolylboronic acid	
155	(2-Hydroxyphenyl)boronic acid	
156	4-Cyanophenylboronic acid	
157	(2-Hydroxymethylphenyl)boronic acid dehydrate	
158	5-(*tert*-Butyldimethylsilanyloxymethyl)pyridine-3-boronic acid	
159	4-Chlorophenylboronic acid	
160	2-Chlorophenylboronic acid	
161	3-Chlorophenylboronic acid	
162	Benzo[B]furan-2-boronic acid	

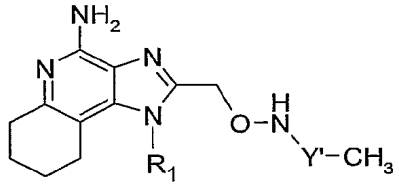
163	3-Acetylphenylboronic acid	
164	(3-Aminocarbonylphenyl)boronic acid	
165	4-(*N*,*N*-Dimethylamino)phenylboronic acid	
166	4-Isopropoxyphenylboronic acid	
167	4-(Pyrrolidine-1-carbonyl)phenylboronic acid	

Exemplary Compounds

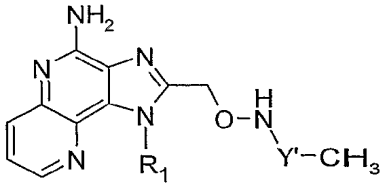
Certain exemplary compounds, including some of those described above in the Examples, have the following Formulas (IIIc, IVc, Va, and VIa) and the following Y' and R_1 substituents, wherein each line of the table is matched with Formula IIIc, IVc, Va, or VIa to represent a specific embodiment of the invention.



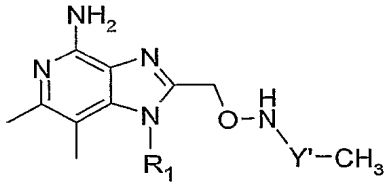
IIIc



IVc



Va



VIa

Y'	R_1
-C(O)-	2-methylpropyl
-C(O)-	2-hydroxy-2-methylpropyl
-C(O)-	2-methyl-2-[(methylsulfonyl)amino]propyl
-C(O)-	4-[(methylsulfonyl)amino]butyl
$-S(O)_2-$	2-methylpropyl
$-S(O)_2-$	2-hydroxy-2-methylpropyl
$-S(O)_2-$	2-methyl-2-[(methylsulfonyl)amino]propyl
$-S(O)_2-$	4-[(methylsulfonyl)amino]butyl
-C(O)-N(H)-	2-methylpropyl
-C(O)-N(H)-	2-hydroxy-2-methylpropyl
-C(O)-N(H)-	2-methyl-2-[(methylsulfonyl)amino]propyl
-C(O)-N(H)-	4-[(methylsulfonyl)amino]butyl

CYTOKINE INDUCTION IN HUMAN CELLS

Compounds of the invention have been found to induce cytokine biosynthesis when tested using the method described below.

An in vitro human blood cell system is used to assess cytokine induction. Activity is based on the measurement of interferon (α) and tumor necrosis factor (α) (IFN-α and TNF-α, respectively) secreted into culture media as described by Testerman et. al. in "Cytokine Induction by the Immunomodulators Imiquimod and S-27609", *Journal of Leukocyte Biology*, *58*, 365-372 (September, 1995).

Blood Cell Preparation for Culture

Whole blood from healthy human donors is collected by venipuncture into EDTA vacutainer tubes. Peripheral blood mononuclear cells (PBMC) are separated from whole blood by density gradient centrifugation using HISTOPAQUE-1077. Blood is diluted 1:1 with Dulbecco's Phosphate Buffered Saline (DPBS) or Hank's Balanced Salts Solution (HBSS). The PBMC layer is collected and washed twice with DPBS or HBSS and resuspended at 4 x 10^6 cells/mL in RPMI complete. The PBMC suspension is added to 48 well flat bottom sterile tissue culture plates (Costar, Cambridge, MA or Becton Dickinson Labware, Lincoln Park, NJ) containing an equal volume of RPMI complete media containing test compound.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. The compounds are generally tested at concentrations ranging from 30-0.014 μM.

Incubation

The solution of test compound is added at 60 μM to the first well containing RPMI complete and serial 3 fold dilutions are made in the wells. The PBMC suspension is then added to the wells in an equal volume, bringing the test compound concentrations to the desired range (30-0.014 μM). The final concentration of PBMC suspension is 2 x 10^6 cells/mL. The plates are covered with sterile plastic lids, mixed gently and then incubated for 18 to 24 hours at 37°C in a 5% carbon dioxide atmosphere.

Separation

Following incubation the plates are centrifuged for 10 minutes at 1000 rpm (approximately 200 x g) at 4°C. The cell-free culture supernatant is removed with a sterile polypropylene pipet and transferred to sterile polypropylene tubes. Samples are maintained at –30 to -70°C until analysis. The samples are analyzed for interferon (α) by ELISA and for tumor necrosis factor (α) by ELISA or IGEN Assay.

Interferon (α) and Tumor Necrosis Factor (α) Analysis by ELISA

Interferon (α) concentration is determined by ELISA using a Human Multi-Species kit from PBL Biomedical Laboratories, New Brunswick, NJ. Results are expressed in pg/mL.

Tumor necrosis factor (α) (TNF) concentration is determined using ELISA kits available from Biosource International, Camarillo, CA. Alternately, the TNF concentration can be determined by ORIGEN M-Series Immunoassay and read on an IGEN M-8 analyzer from IGEN International, Gaithersburg, MD. The immunoassay uses a human TNF capture and detection antibody pair from Biosource International, Camarillo, CA. Results are expressed in pg/mL.

Certain compounds of the invention may modulate cytokine biosynthesis by inhibiting production of tumor necrosis factor α (TNF-α) when tested using the method described below.

TNF-α INHIBITION IN MOUSE CELLS

The mouse macrophage cell line Raw 264.7 is used to assess the ability of compounds to inhibit tumor necrosis factor-α (TNF-α) production upon stimulation by lipopolysaccharide (LPS).

Single Concentration Assay:

Blood Cell Preparation for Culture

Raw cells (ATCC) are harvested by gentle scraping and then counted. The cell suspension is brought to 3 x 10^5 cells/mL in RPMI with 10 % fetal bovine serum (FBS). Cell suspension (100 µL) is added to 96-well flat bottom sterile tissues culture plates (Becton Dickinson Labware, Lincoln Park, NJ). The final concentration of cells is 3 x 10^4 cells/well. The plates are incubated for 3 hours. Prior to the addition of test compound the medium is replaced with colorless RPMI medium with 3 % FBS.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. Compounds are tested at 5μM. LPS (Lipopolysaccaride from *Salmonella typhimurium*, Sigma-Aldrich) is diluted with colorless RPMI to the EC_{70} concentration as measured by a dose response assay.

Incubation

A solution of test compound (1μl) is added to each well. The plates are mixed on a microtiter plate shaker for 1 minute and then placed in an incubator. Twenty minutes later the solution of LPS (1 μL, EC_{70} concentration ~ 10 ng/ml) is added and the plates are mixed for 1 minute on a shaker. The plates are incubated for 18 to 24 hours at 37 °C in a 5 % carbon dioxide atmosphere.

TNF-α Analysis

Following the incubation the supernatant is removed with a pipet. TNF-α concentration is determined by ELISA using a mouse TNF- α kit (from Biosource International, Camarillo, CA). Results are expressed in pg/mL. TNF-α expression upon LPS stimulation alone is considered a 100% response.

Dose Response Assay:

Blood Cell Preparation for Culture

Raw cells (ATCC) are harvested by gentle scraping and then counted. The cell suspension is brought to 4 x 10^5 cells/mL in RPMI with 10 % FBS. Cell suspension (250 μL) is added to 48-well flat bottom sterile tissues culture plates (Costar, Cambridge, MA). The final concentration of cells is 1 x 10^5 cells/well. The plates are incubated for 3 hours. Prior to the addition of test compound the medium is replaced with colorless RPMI medium with 3 % FBS.

Compound Preparation

The compounds are solubilized in dimethyl sulfoxide (DMSO). The DMSO concentration should not exceed a final concentration of 1% for addition to the culture wells. Compounds are tested at 0.03, 0.1, 0.3, 1, 3, 5 and 10 μM. LPS (Lipopolysaccaride from *Salmonella typhimurium*, Sigma-Aldrich) is diluted with colorless RPMI to the EC_{70} concentration as measured by dose response assay.

Incubation

A solution of test compound (200 μl) is added to each well. The plates are mixed on a microtiter plate shaker for 1 minute and then placed in an incubator. Twenty minutes later the solution of LPS (200 μL, EC_{70} concentration ~ 10 ng/ml) is added and the plates are mixed for 1 minute on a shaker. The plates are incubated for 18 to 24 hours at 37 °C in a 5 % carbon dioxide atmosphere.

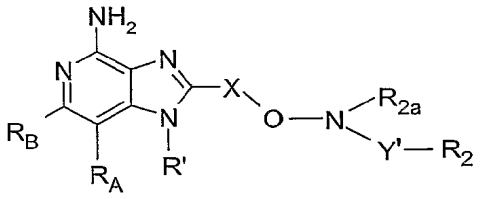
TNF-α Analysis

Following the incubation the supernatant is removed with a pipet. TNF-α concentration is determined by ELISA using a mouse TNF- α kit (from Biosource International, Camarillo, CA). Results are expressed in pg/mL. TNF-α expression upon LPS stimulation alone is considered a 100% response.

The complete disclosures of the patents, patent documents, and publications cited herein are incorporated by reference in their entirety as if each were individually incorporated. Various modifications and alterations to this invention will become apparent to those skilled in the art without departing from the scope and spirit of this invention. It should be understood that this invention is not intended to be unduly limited by the illustrative embodiments and examples set forth herein and that such examples and embodiments are presented by way of example only with the scope of the invention intended to be limited only by the claims set forth herein as follows.

WHAT IS CLAIMED IS:

1. A compound of the Formula I:



I

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

R_A and R_B are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

or when taken together, R_A and R_B form a fused aryl ring or heteroaryl ring containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R''' groups;

or when taken together, R_A and R_B form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

Y' is selected from the group consisting of:

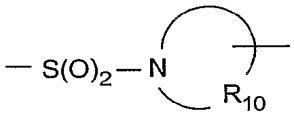
a bond,

-C(O)-,

-C(S)-,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,



,

-C(O)-O-,

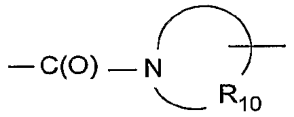
$-C(O)-N(R_8)-$,

$-C(S)-N(R_8)-$,

$-C(O)-N(R_8)-S(O)_2-$,

$-C(O)-N(R_8)-C(O)-$,

$-C(S)-N(R_8)-C(O)-$,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

$-C(=NH)-N(R_8)-$;

R_2 and R_{2a} are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

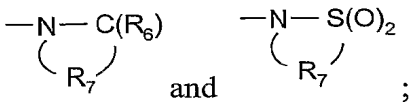
heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
-$S(O)_{0-2}$-alkyl,
-$S(O)_{0-2}$-aryl,
-NH-$S(O)_2$-alkyl,
-NH-$S(O)_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-$N(R_8)_2$,
-$N(R_8)$-C(O)-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

or R_2 and R_{2a} together with the nitrogen atom and Y' to which they are bonded can join to form a ring selected from the group consisting of:



and ;

R' is hydrogen or a non-interfering substituent;

R''' is a non-interfering substituent;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

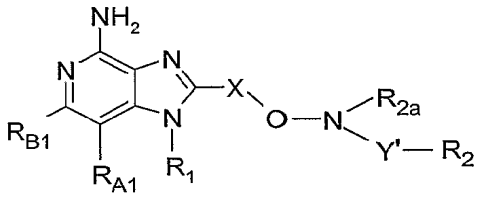
R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl; and

R_{10} is C_{3-8} alkylene;

or a pharmaceutically acceptable salt thereof.

2. A compound of the Formula II:



II

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

R_{A1} and R_{B1} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

or when taken together, R_{A1} and R_{B1} form a fused aryl ring or heteroaryl ring

containing one heteroatom selected from the group consisting of N and S, wherein the aryl or heteroaryl ring is unsubstituted or substituted by one or more R groups, or substituted by one R_3 group, or substituted by one R_3 group and one R group;

or when taken together, R_{A1} and R_{B1} form a fused 5 to 7 membered saturated ring, optionally containing one heteroatom selected from the group consisting of N and S, and unsubstituted or substituted by one or more R groups;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X'-R_4$,

$-Z-X'-Y-R_4$,

$-Z-X'-Y-X'-Y-R_4$, and

$-Z-X'-R_5$;

Y' is selected from the group consisting of:

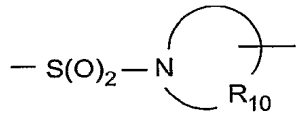
a bond,

-C(O)-,

-C(S)-,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,



,

-C(O)-O-,

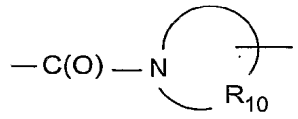
$-C(O)-N(R_8)-$,

-C(S)-N(R_8)-,

-C(O)-N(R_8)-S(O)$_2$-,

-C(O)-N(R_8)-C(O)-,

-C(S)-N(R_8)-C(O)-,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

-C(=NH)-N(R_8)-;

R_1 is selected from the group consisting of:

-R_4,

-X'-R_4,

-X'-Y-R_4,

-X'-Y-X'-Y-R_4,

-X'-R_5,

-X"-O-NR_{1a}-Y'-R_{1b}, and

-X"-O-N=C(R_1')(R_1");

R_{1a}, R_{1b}, R_1', R_1", R_2, and R_{2a} are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

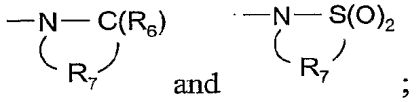
heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

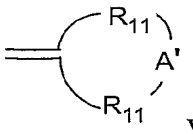
hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
-S(O)$_{0-2}$-alkyl,
-S(O)$_{0-2}$-aryl,
-NH-S(O)$_2$-alkyl,
-NH-S(O)$_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R_8)$_2$,
-N(R_8)-C(O)-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

or R_{1a} and R_{1b} and/or R_2 and R_{2a} together with the nitrogen atom and Y' to which they are bonded can join to form a ring selected from the group consisting of:

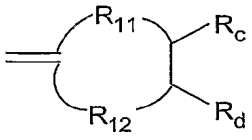

and

;

or R_1' and R_1" can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X" is $-CH(R_{13})$-alkylene- or $-CH(R_{13})$-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

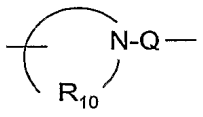
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

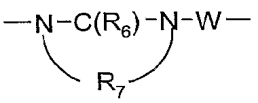
$-C(R_6)-N(R_8)-$,

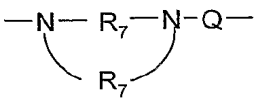
$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



,


,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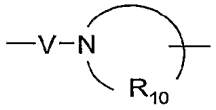
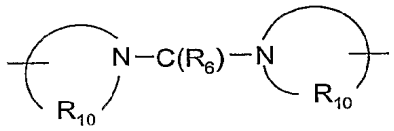
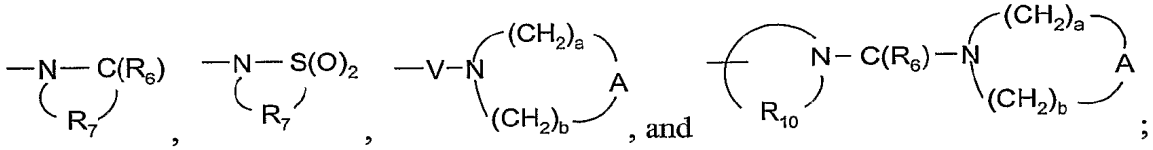

, and


;

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

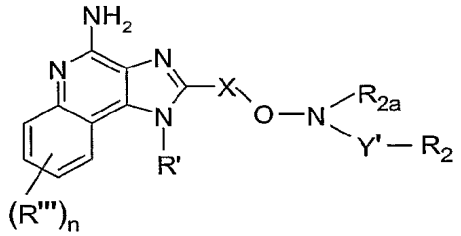
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$;

or a pharmaceutically acceptable salt thereof.

3. A compound of the Formula III:



III

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

Y' is selected from the group consisting of:

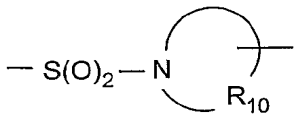
a bond,

-C(O)-,

-C(S)-,

-$S(O)_2$-,

-$S(O)_2$-$N(R_8)$-,



,

-C(O)-O-,

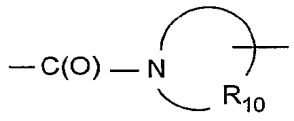
-$C(O)$-$N(R_8)$-,

-$C(S)$-$N(R_8)$-,

-$C(O)$-$N(R_8)$-$S(O)_2$-,

-$C(O)$-$N(R_8)$-C(O)-,

-$C(S)$-$N(R_8)$-C(O)-,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

-$C(=NH)$-$N(R_8)$-;

R_2 and R_{2a} are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
$-S(O)_{0-2}$-alkyl,
$-S(O)_{0-2}$-aryl,
$-NH-S(O)_2$-alkyl,
$-NH-S(O)_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
$-C(O)-N(R_8)_2$,
$-N(R_8)-C(O)$-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_{10} is C_{3-8} alkylene;

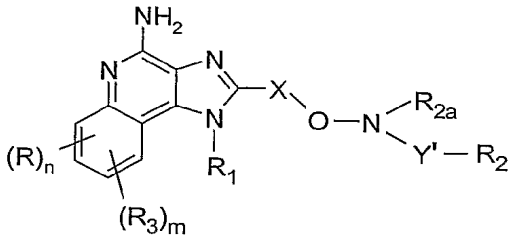
n is an integer from 0 to 4;

R''' is a non-interfering substituent; and

R' is hydrogen or a non-interfering substituent;

or a pharmaceutically acceptable salt thereof.

4. A compound of the Formula IIIa:



IIIa

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

Y' is selected from the group consisting of:

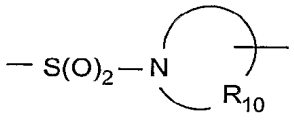
a bond,

-C(O)-,

-C(S)-,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,



,

-C(O)-O-,

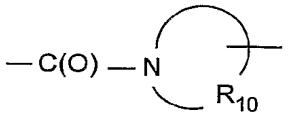
$-C(O)-N(R_8)-$,

$-C(S)-N(R_8)-$,

$-C(O)-N(R_8)-S(O)_2-$,

$-C(O)-N(R_8)-C(O)-$,

$-C(S)-N(R_8)-C(O)-$,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

$-C(=NH)-N(R_8)-$;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_1 is selected from the group consisting of:

$-R_4$,

$-X'-R_4$,

$-X'-Y-R_4$,

$-X'-Y-X'-Y-R_4$,

$-X'-R_5$,

$-X''-O-NR_{1a}-Y'-R_{1b}$, and

$-X''-O-N=C(R_1')(R_1'')$;

R_{1a}, R_{1b}, R_1', R_1'', R_2, and R_{2a} are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

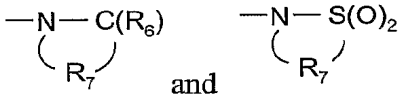
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

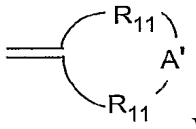
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
$-S(O)_{0-2}$-alkyl,
$-S(O)_{0-2}$-aryl,
$-NH-S(O)_2$-alkyl,
$-NH-S(O)_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
$-C(O)-N(R_8)_2$,
$-N(R_8)-C(O)$-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

or R_{1a} and R_{1b} and/or R_2 and R_{2a} together with the nitrogen atom and Y' to which they are bonded can join to form a ring selected from the group consisting of:

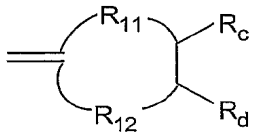

and

;

or R_1' and R_1" can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

R_3 is selected from the group consisting of:

-Z-R_4,

-Z-X'-R_4,

-Z-X'-Y-R_4,

-Z-X'-Y-X'-Y-R_4, and

-Z-X'-R_5;

n is an integer from 0 to 4;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X" is $-CH(R_{13})$-alkylene- or $-CH(R_{13})$-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

-$S(O)_{0-2}$-,

-$S(O)_2$-$N(R_8)$-,

-$C(R_6)$-,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

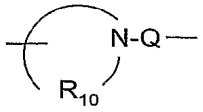
-O-C(O)-O-,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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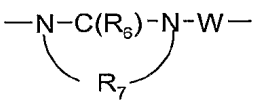

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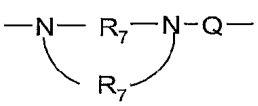

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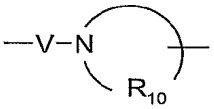
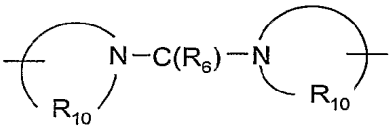


, and

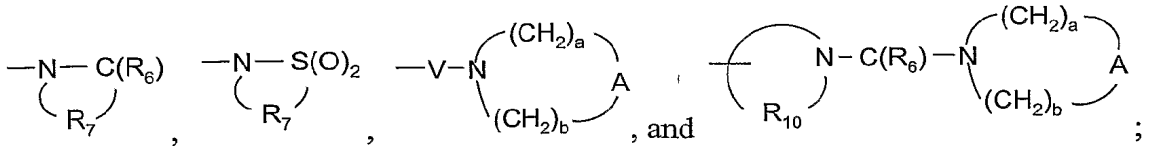


;

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

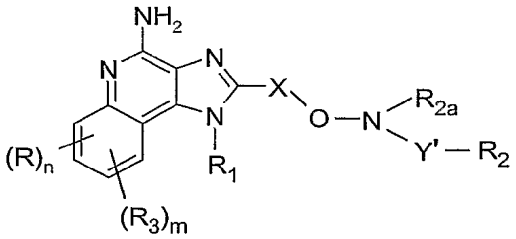
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

5. A compound of the Formula IIIa:



IIIa

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

Y' is selected from the group consisting of:

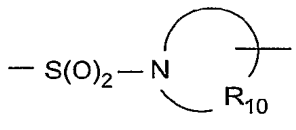
a bond,

-C(O)-,

-C(S)-,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,



,

-C(O)-O-,

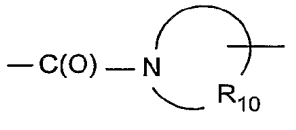
$-C(O)-N(R_8)-$,

$-C(S)-N(R_8)-$,

$-C(O)-N(R_8)-S(O)_2-$,

$-C(O)-N(R_8)-C(O)-$,

$-C(S)-N(R_8)-C(O)-$,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

$-C(=NH)-N(R_8)-$;

R_2 and R_{2a} are independently selected from the group consisting of:

hydrogen,

alkyl,
alkenyl,
aryl,
arylalkylenyl,
heteroaryl,
heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:
hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
$-S(O)_{0-2}$-alkyl,
$-S(O)_{0-2}$-aryl,
$-NH-S(O)_2$-alkyl,
$-NH-S(O)_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,

-C(O)-N(R_8)$_2$,
-N(R_8)-C(O)-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

R is selected from the group consisting of:
halogen,
hydroxy,
alkyl,
alkenyl,
haloalkyl,
alkoxy,
alkylthio, and
-N(R_9)$_2$;

R_1 is selected from the group consisting of:
-R_4,
-X'-R_4,
-X'-Y-R_4,
-X'-Y-X'-Y-R_4,
-X'-R_5,
-X''-O-NH-Y'-R_1', and
-X''-O-N=C(R_1')(R_1'');

R_3 is selected from the group consisting of:
-Z-R_4,
-Z-X'-R_4,
-Z-X'-Y-R_4,
-Z-X'-Y-X'-Y-R_4, and
-Z-X'-R_5;

n is an integer from 0 to 4;

m is 0 or 1; with the proviso that when m is 1, then n is 0 or 1;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and

alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X" is $-CH(R_{13})$-alkylene- or $-CH(R_{13})$-alkenylene-;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

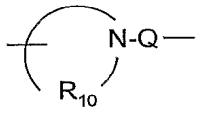
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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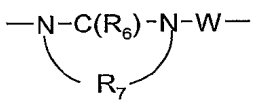

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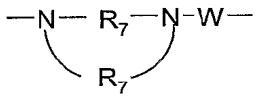
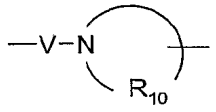
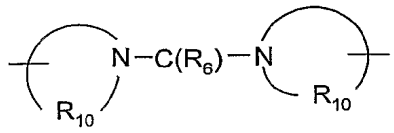


,



, and



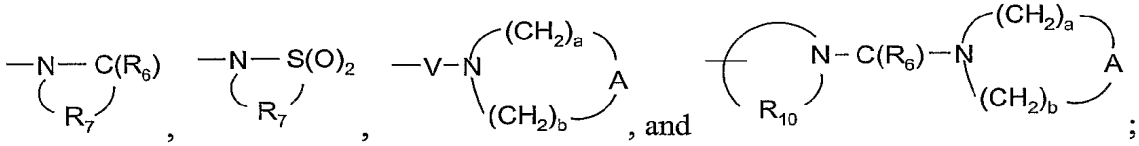
;

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl,

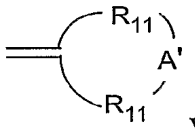
heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:

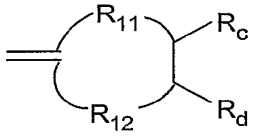


;

R_1', and R_1'' are independently the same as R_2, or R_1' and R_1'' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

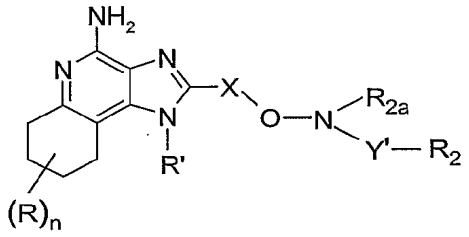
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

6. A compound of the Formula IV:



IV

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

Y' is selected from the group consisting of:

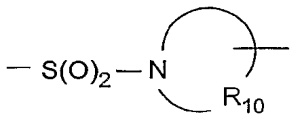
a bond,

-C(O)-,

-C(S)-,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,



,

-C(O)-O-,

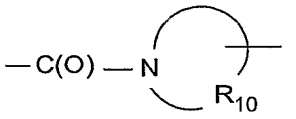
-C(O)-N(R_8)-,

-C(S)-N(R_8)-,

-C(O)-N(R_8)-S(O)$_2$-,

-C(O)-N(R_8)-C(O)-,

-C(S)-N(R_8)-C(O)-,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

-C(=NH)-N(R_8)-;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

–N(R_9)$_2$;

n is an integer from 0 to 4;

R_2 and R_{2a} are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,
heterocyclyl,
heterocyclylalkylenyl, and
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
-$S(O)_{0-2}$-alkyl,
-$S(O)_{0-2}$-aryl,
-NH-$S(O)_2$-alkyl,
-NH-$S(O)_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy;
-C(O)-O-alkyl,
-$C(O)$-$N(R_8)_2$,
-$N(R_8)$-C(O)-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl,

C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

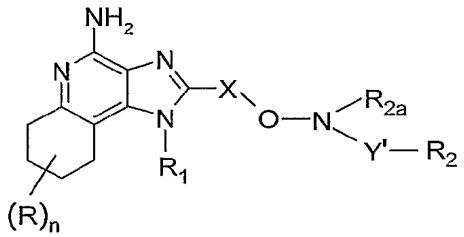
R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene; and

R' is hydrogen or a non-interfering substituent;

or a pharmaceutically acceptable salt thereof.

7. A compound of the Formula (IVa):



IVa

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

Y' is selected from the group consisting of:

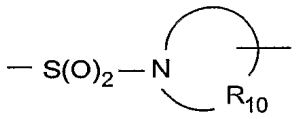
a bond,

-C(O)-,

-C(S)-,

-$S(O)_2$-,

-$S(O)_2$-$N(R_8)$-,



,

-C(O)-O-,

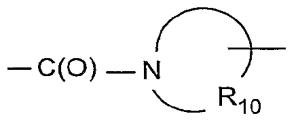
-C(O)-$N(R_8)$-,

-C(S)-$N(R_8)$-,

-C(O)-$N(R_8)$-$S(O)_2$-,

-C(O)-$N(R_8)$-C(O)-,

-C(S)-$N(R_8)$-C(O)-,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

-C(=NH)-N(R_8)-;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

R_1 is selected from the group consisting of:

-R_4,

-X'-R_4,

-X'-Y-R_4,

-X'-Y-X'-Y-R_4,

-X'-R_5,

-X"-O-NR_{1a}-Y'-R_{1b}, and

-X"-O-N=C(R_1')(R_1");

R_{1a}, R_{1b}, R_1', R_1", R_2, and R_{2a} are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,

dialkylamino,

-$S(O)_{0-2}$-alkyl,

-$S(O)_{0-2}$-aryl,

-NH-$S(O)_2$-alkyl,

-NH-$S(O)_2$-aryl,

haloalkoxy,

halogen,

cyano,

nitro,

aryl,

heteroaryl,

heterocyclyl,

aryloxy,

arylalkyleneoxy,

-C(O)-O-alkyl,

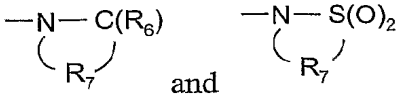
-$C(O)$-$N(R_8)_2$,

-$N(R_8)$-C(O)-alkyl,

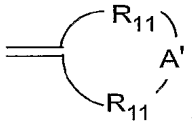
-O-(CO)-alkyl, and

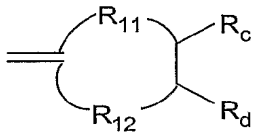
-C(O)-alkyl;

or R_{1a} and R_{1b} and/or R_2 and R_{2a} together with the nitrogen atom and Y' to which they are bonded can join to form a ring selected from the group consisting of:


and ;

or R_1' and R_1'' can join together to form a ring system selected from the group consisting of:


wherein the total number of atoms in the ring is 4 to 9, and


wherein the total number of atoms in the ring is 4 to 9;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

n is an integer from 0 to 4;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X" is $-CH(R_{13})$-alkylene- or $-CH(R_{13})$-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

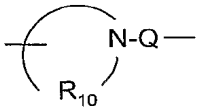
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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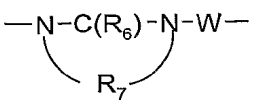

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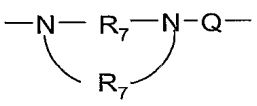

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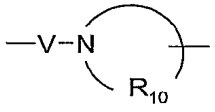
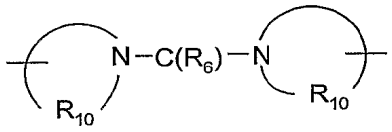


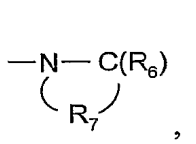
, and



;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



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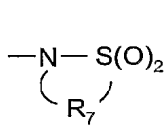

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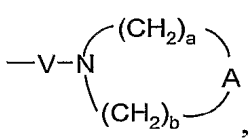
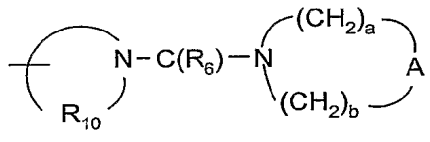


, and



;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl,

C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

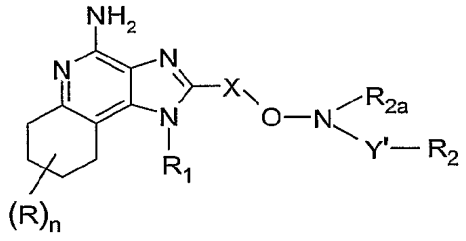
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$;

or a pharmaceutically acceptable salt thereof.

8. A compound of the Formula IVa:



IVa

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

Y' is selected from the group consisting of:

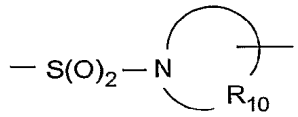
a bond,

-C(O)-,

-C(S)-,

-$S(O)_2$-,

-$S(O)_2$-$N(R_8)$-,



,

-C(O)-O-,

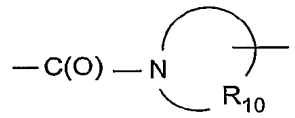
-$C(O)$-$N(R_8)$-,

-$C(S)$-$N(R_8)$-,

-$C(O)$-$N(R_8)$-$S(O)_2$-,

-$C(O)$-$N(R_8)$-C(O)-,

-$C(S)$-$N(R_8)$-C(O)-,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

-C(=NH)-$N(R_8)$-;

R_2 and R_{2a} are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
-S(O)$_{0-2}$-alkyl,
-S(O)$_{0-2}$-aryl,
-NH-S(O)$_2$-alkyl,
-NH-S(O)$_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy;
-C(O)-O-alkyl,
-C(O)-N(R_8)$_2$,
-N(R_8)-C(O)-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

R is selected from the group consisting of:
halogen,
hydroxy,
alkyl,
alkenyl,
haloalkyl,
alkoxy,

alkylthio, and

$-N(R_9)_2$;

n is an integer from 0 to 4;

R_1 is selected from the group consisting of:

$-R_4$,

$-X'-R_4$,

$-X'-Y-R_4$,

$-X'-Y-X'-Y-R_4$,

$-X'-R_5$,

$-X''-O-NH-Y'-R_1'$, and

$-X''-O-N=C(R_1')(R_1'')$;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X'' is $-CH(R_{13})$-alkylene- or $-CH(R_{13})$-alkenylene-;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

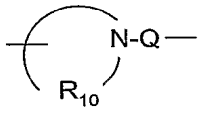
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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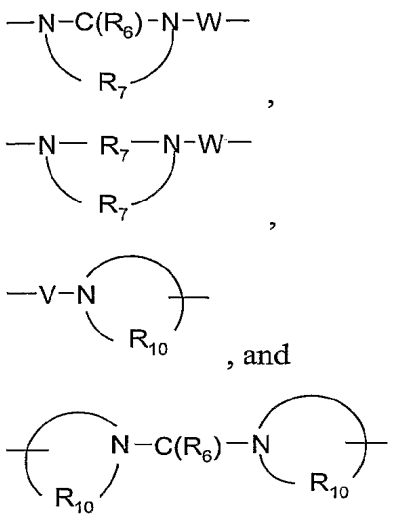
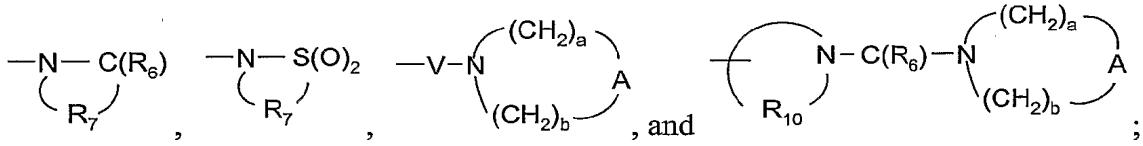
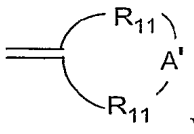


R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

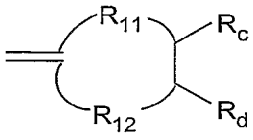
R_5 is selected from the group consisting of:



R_1' and R_1'' are independently R_2, or R_1' and R_1'' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-CH_2$-, -O-, -C(O)-, $-S(O)_{0-2}$-, and $-N(R_4)$-;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}$-, $-N(-Q-R_4)$-, and $-CH_2$-;

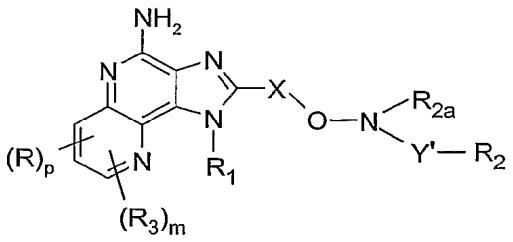
Q is selected from the group consisting of a bond, $-C(R_6)$-, $-C(R_6)-C(R_6)$-, $-S(O)_2$-, $-C(R_6)-N(R_8)-W$-, $-S(O)_2-N(R_8)$-, $-C(R_6)-O$-, and $-C(R_6)-N(OR_9)$-;

V is selected from the group consisting of $-C(R_6)$-, $-O-C(R_6)$-, $-N(R_8)-C(R_6)$-, and $-S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7; or a pharmaceutically acceptable salt thereof.

9. A compound of the Formula V:



V

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

Y' is selected from the group consisting of:

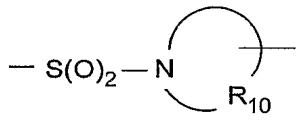
a bond,

-C(O)-,

-C(S)-,

-$S(O)_2$-,

-$S(O)_2$-$N(R_8)$-,



,

-C(O)-O-,

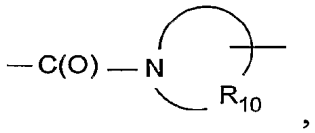
-C(O)-$N(R_8)$-,

-C(S)-$N(R_8)$-,

-C(O)-$N(R_8)$-$S(O)_2$-,

-C(O)-$N(R_8)$-C(O)-,

-C(S)-$N(R_8)$-C(O)-,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

-C(=NH)-N(R_8)-;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

-N(R_9)$_2$;

R_1 is selected from the group consisting of:

-R_4,

-X'-R_4,

-X'-Y-R_4,

-X'-Y-X'-Y-R_4,

-X'-R_5,

-X"-O-NR_{1a}-Y'-R_{1b}, and

-X"-O-N=C(R_1')(R_1");

R_{1a}, R_{1b}, R_1', R_1", R_2, and R_{2a} are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

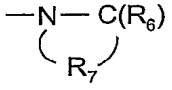
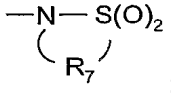
heterocyclyl,

heterocyclylalkylenyl, and

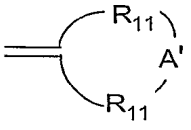
alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,
alkyl,
haloalkyl,
hydroxyalkyl,
alkoxy,
dialkylamino,
$-S(O)_{0-2}$-alkyl,
$-S(O)_{0-2}$-aryl,
$-NH-S(O)_2$-alkyl,
$-NH-S(O)_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
$-C(O)-N(R_8)_2$,
$-N(R_8)-C(O)$-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

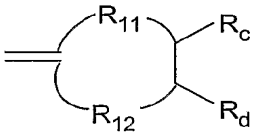
or R_{1a} and R_{1b} and/or R_2 and R_{2a} together with the nitrogen atom and Y' to which they are bonded can join to form a ring selected from the group consisting of:

 and  ;

or R_1' and R_1'' can join together to form a ring system selected from the group consisting of:



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X'-R_4$,

$-Z-X'-Y-R_4$,

$-Z-X'-Y-X'-Y-R_4$, and

$-Z-X'-R_5$;

p is an integer from 0 to 3;

m is 0 or 1, with the proviso that when m is 1, p is 0 or 1;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X'' is $-CH(R_{13})$-alkylene- or $-CH(R_{13})$-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

-O-C(R_6)-,

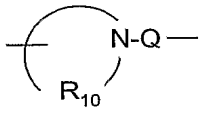
-O-C(O)-O-,

-N(R_8)-Q-,

-C(R_6)-N(R_8)-,

-O-C(R_6)-N(R_8)-,

-C(R_6)-N(OR_9)-,



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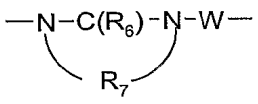

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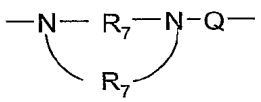

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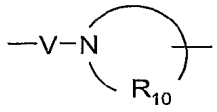
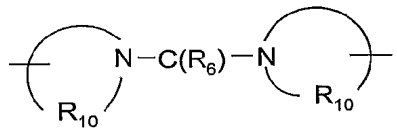


, and

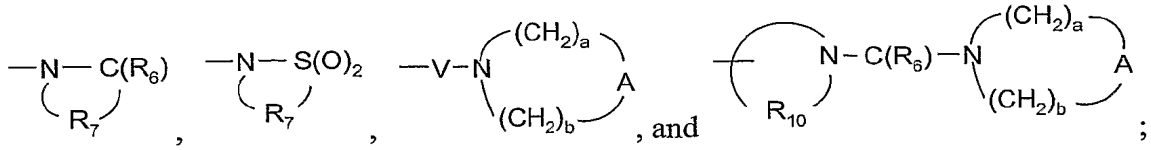


;

Z is a bond or -O-;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:



R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

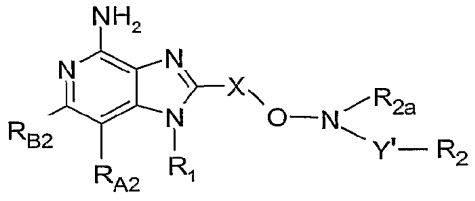
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7;

or a pharmaceutically acceptable salt thereof.

10. A compound of the Formula VI:



VI

wherein:

X is C_{1-10} alkylene or C_{2-10} alkenylene;

R_{A2} and R_{B2} are each independently selected from the group consisting of:

hydrogen,

halogen,

alkyl,

alkenyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

Y' is selected from the group consisting of:

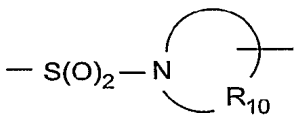
a bond,

-C(O)-,

-C(S)-,

$-S(O)_2-$,

$-S(O)_2-N(R_8)-$,



,

-C(O)-O-,

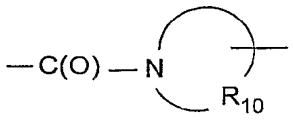
$-C(O)-N(R_8)-$,

$-C(S)-N(R_8)-$,

$-C(O)-N(R_8)-S(O)_2-$,

$-C(O)-N(R_8)-C(O)-$,

$-C(S)-N(R_8)-C(O)-$,



,

-C(O)-C(O)-,

-C(O)-C(O)-O-, and

-C(=NH)-N(R_8)-;

R_1 is selected from the group consisting of:

-R_4,

-X'-R_4,

-X'-Y-R_4,

-X'-Y-X'-Y-R_4,

-X'-R_5,

-X"-O-NR_{1a}-Y'-R_{1b}, and

-X"-O-N=C(R_1')(R_1");

R_{1a}, R_{1b}, R_1', R_1", R_2, and R_{2a} are independently selected from the group consisting of:

hydrogen,

alkyl,

alkenyl,

aryl,

arylalkylenyl,

heteroaryl,

heteroarylalkylenyl,

heterocyclyl,

heterocyclylalkylenyl, and

alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of:

hydroxy,

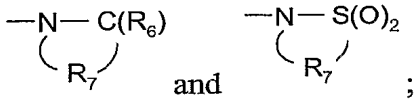
alkyl,

haloalkyl,

hydroxyalkyl,

alkoxy,
dialkylamino,
-S(O)$_{0-2}$-alkyl,
-S(O)$_{0-2}$-aryl,
-NH-S(O)$_2$-alkyl,
-NH-S(O)$_2$-aryl,
haloalkoxy,
halogen,
cyano,
nitro,
aryl,
heteroaryl,
heterocyclyl,
aryloxy,
arylalkyleneoxy,
-C(O)-O-alkyl,
-C(O)-N(R_8)$_2$,
-N(R_8)-C(O)-alkyl,
-O-(CO)-alkyl, and
-C(O)-alkyl;

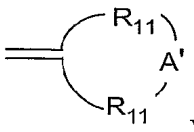
or R_{1a} and R_{1b} and/or R_2 and R_{2a} together with the nitrogen atom and Y' to which they are bonded can join to form a ring selected from the group consisting of:

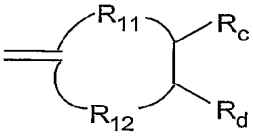


and

;

or R_1' and R_1" can join together to form a ring system selected from the group consisting of:


wherein the total number of atoms in the ring is 4 to 9, and


wherein the total number of atoms in the ring is 4 to 9;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four heteroatoms;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X" is $-CH(R_{13})$-alkylene- or $-CH(R_{13})$-alkenylene-, wherein the alkylene and alkenylene are optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

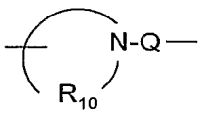
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,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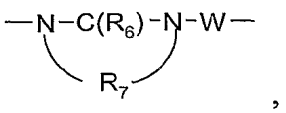
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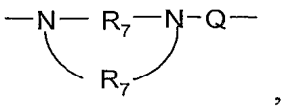
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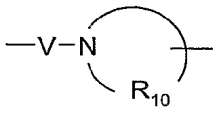
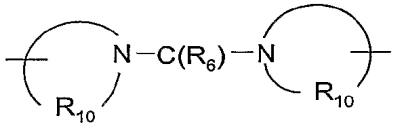
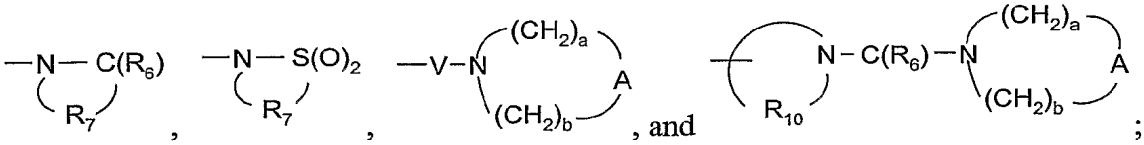

, and


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of:


;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}-$, $-N(-Q-R_4)-$, and $-CH_2-$;

Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that $a + b \leq 7$;

or a pharmaceutically acceptable salt thereof.

11. The compound or salt of claim 9 wherein p is 0.

12. The compound or salt of any one of claims 4, 5, 9, or 11 wherein m is 0.

13. The compound or salt of any one of claims 3 through 8, or claim 12 as dependent on any one of claims 4 or 5, wherein n is 0.

14. The compound or salt of any one of claims 4 or 5 or claim 13 as dependent on any one of claims 4, 5, or 12 wherein m and n are 0.

15. The compound or salt of claim 9 or claim 12 as dependent on any one of claims 9 or 11 wherein p and m are 0.

16. The compound or salt of claim 10 wherein R_{A2} and R_{B2} are each methyl.

17. The compound or salt of any one of claims 1, 3, or 6, or claim 13 as dependent on any one of claims 3 or 6, wherein R' is selected from the group consisting of:

$-R_4$,

$-X'-R_4$,

$-X'-Y-R_4$,

$-X'-Y-X'-Y-R_4$,

$-X'-R_5$,

$-X''-O-NH-Y'-R_1'$, and

$-X''-O-N=C(R_1')(R_1'')$;

wherein:

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

X'' is $-CH(R_{13})$alkylene or $-CH(R_{13})$alkenylene;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

$-C(R_6)-O-$,

$-O-C(R_6)-$,

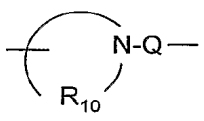
$-O-C(O)-O-$,

$-N(R_8)-Q-$,

$-C(R_6)-N(R_8)-$,

$-O-C(R_6)-N(R_8)-$,

$-C(R_6)-N(OR_9)-$,



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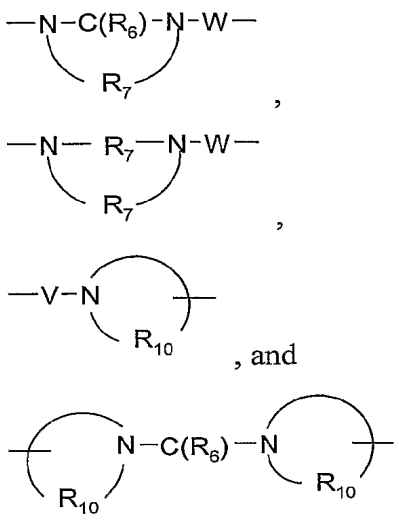
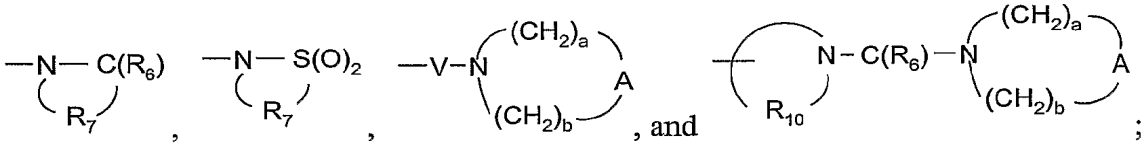
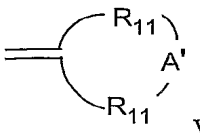


R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

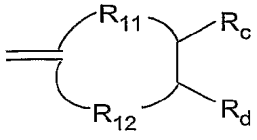
R_5 is selected from the group consisting of



R_1' and R_1'' are independently R_2, or R_1' and R_1'' can join together to form a ring system selected from the group consisting of



wherein the total number of atoms in the ring is 4 to 9, and



wherein the total number of atoms in the ring is 4 to 9;

R_c and R_d are independently selected from the group consisting of hydrogen, halogen, hydroxy, alkyl, alkenyl, aryl, haloalkyl, alkoxy, alkylthio, and $-N(R_9)_2$; or R_c and R_d can join to form a fused aryl ring or fused 5-10 membered heteroaryl ring containing one to four hetero atoms;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

R_{11} is C_{1-6} alkylene or C_{2-6} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{12} is selected from the group consisting of a bond, C_{1-5} alkylene, and C_{2-5} alkenylene, wherein the alkylene or alkenylene is optionally interrupted by one heteroatom;

R_{13} is selected from the group consisting of hydrogen and alkyl which may be optionally interrupted by one or more -O- groups;

A is selected from the group consisting of $-CH_2$-, -O-, -C(O)-, $-S(O)_{0-2}$-, and $-N(R_4)$-;

A' is selected from the group consisting of -O-, $-S(O)_{0-2}$-, -N(-Q-R_4)-. and $-CH_2$-;

Q is selected from the group consisting of a bond, $-C(R_6)$-, $-C(R_6)-C(R_6)$-, $-S(O)_2$-, $-C(R_6)-N(R_8)$-W-, $-S(O)_2-N(R_8)$-, $-C(R_6)-O$-, and $-C(R_6)-N(OR_9)$-;

V is selected from the group consisting of $-C(R_6)$-, $-O-C(R_6)$-, $-N(R_8)-C(R_6)$-, and $-S(O)_2$-;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2$-; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

18. The compound or salt of claim 1, claim 3, or claim 17 as dependent on any one of claims 1 or 3 wherein:

R''' is R or R_3 when n is 1, R or one R and one R_3 when n is 2, or R when n is 3 to 4;

R is selected from the group consisting of:

halogen,

hydroxy,

alkyl,

alkenyl,

haloalkyl,

alkoxy,

alkylthio, and

$-N(R_9)_2$;

R_3 is selected from the group consisting of:

$-Z-R_4$,

$-Z-X'-R_4$,

$-Z-X'-Y-R_4$,

$-Z-X'-Y-X'-Y-R_4$, and

$-Z-X'-R_5$;

n is 0 to 4;

Z is a bond or -O-;

X' is selected from the group consisting of alkylene, alkenylene, alkynylene, arylene, heteroarylene, and heterocyclylene wherein the alkylene, alkenylene, and alkynylene groups can be optionally interrupted or terminated by arylene, heteroarylene or heterocyclylene and optionally interrupted by one or more -O- groups;

Y is selected from the group consisting of:

$-S(O)_{0-2}-$,

$-S(O)_2-N(R_8)-$,

$-C(R_6)-$,

-$C(R_6)$-O-,

-O-$C(R_6)$-,

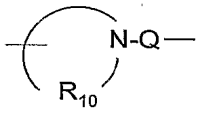
-O-C(O)-O-,

-$N(R_8)$-Q-,

-$C(R_6)$-$N(R_8)$-,

-O-$C(R_6)$-$N(R_8)$-,

-$C(R_6)$-$N(OR_9)$-,



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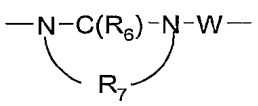

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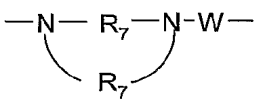

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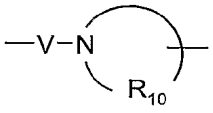

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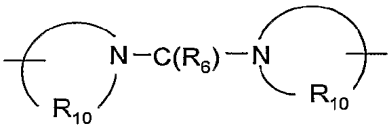
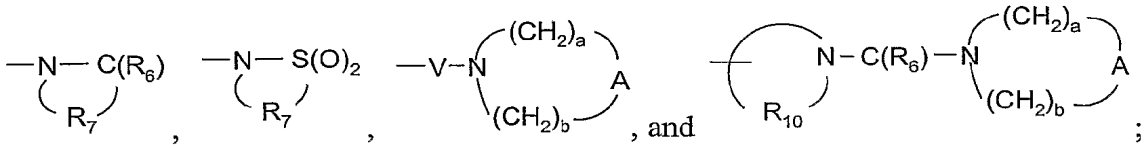


;

R_4 is selected from the group consisting of hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl wherein the alkyl, alkenyl, alkynyl, aryl, arylalkylenyl, aryloxyalkylenyl, alkylarylenyl, heteroaryl, heteroarylalkylenyl, heteroaryloxyalkylenyl, alkylheteroarylenyl, and heterocyclyl groups can be unsubstituted or substituted by one or more substituents independently selected from the group consisting of alkyl, alkoxy, hydroxyalkyl, haloalkyl, haloalkoxy, halogen, nitro, hydroxy, mercapto, cyano, aryl, aryloxy, arylalkyleneoxy, heteroaryl, heteroaryloxy, heteroarylalkyleneoxy, heterocyclyl, amino, alkylamino, dialkylamino, (dialkylamino)alkyleneoxy, and in the case of alkyl, alkenyl, alkynyl, and heterocyclyl, oxo;

R_5 is selected from the group consisting of


, , , and ;

R_6 is selected from the group consisting of =O and =S;

R_7 is C_{2-7} alkylene;

R_8 is selected from the group consisting of hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} alkoxy-C_{1-10} alkylenyl, and aryl-C_{1-10} alkylenyl;

R_9 is selected from the group consisting of hydrogen and alkyl;

R_{10} is C_{3-8} alkylene;

A is selected from the group consisting of $-CH_2-$, -O-, -C(O)-, $-S(O)_{0-2}-$, and $-N(R_4)-$;

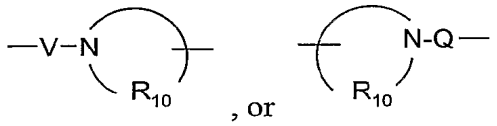
Q is selected from the group consisting of a bond, $-C(R_6)-$, $-C(R_6)-C(R_6)-$, $-S(O)_2-$, $-C(R_6)-N(R_8)-W-$, $-S(O)_2-N(R_8)-$, $-C(R_6)-O-$, and $-C(R_6)-N(OR_9)-$;

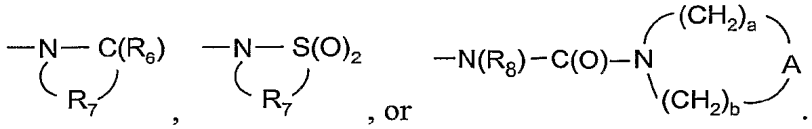
V is selected from the group consisting of $-C(R_6)-$, $-O-C(R_6)-$, $-N(R_8)-C(R_6)-$, and $-S(O)_2-$;

W is selected from the group consisting of a bond, -C(O)-, and $-S(O)_2-$; and

a and b are independently integers from 1 to 6 with the proviso that a + b is ≤ 7.

19. The compound or salt of any one of claims 2, 4, 5, 7 through 12, or 14 through 16, or claim 13 as dependent on any one of claims 4, 5, 7, 8, or 12, wherein R_1 is selected from the group consisting of alkyl, arylalkylenyl, aryloxyalkylenyl, hydroxyalkyl, alkylsulfonylalkylenyl, -X'-Y-R_4, and -X'-R_5; wherein X' is alkylene; Y is $-N(R_8)-C(O)-$, $-N(R_8)-S(O)_2-$, $-N(R_8)-S(O)_2-N(R_8)-$, $-N(R_8)-C(O)-N(R_8)-$, $-N(R_8)-C(O)-N(R_8)-C(O)-$,


; R_4 is hydrogen, alkyl, alkenyl, aryl, or heteroaryl, wherein alkyl and alkenyl are optionally substituted by aryl or aryloxy and wherein aryl is optionally substituted by one or more substituents selected from the group consisting of alkyl, alkoxy, cyano, haloalkyl, and halogen; and R_5 is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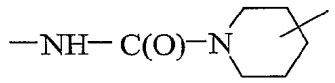
20. The compound or salt of claim 19 wherein R_1 is 2-methylpropyl, 2-hydroxy-2-methylpropyl, or –X'-Y-R_4; X' is ethylene, propylene, or butylene; Y is -NH-C(O)-, -NH-$S(O)_2$-, -NH-$S(O)_2$-N(R_8)-, -NH-C(O)-N(R_8)-, -NH-C(O)-NH-C(O)-, or

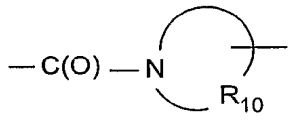


; and R_8 is hydrogen or methyl.

21. The compound or salt of any one of claims 1 through 20 wherein X is C_{1-4} alkylene.

22. The compound or salt of claim 21 wherein X is methylene.

23. The compound or salt of any one of claims 1 through 22 wherein Y' is selected from the group consisting of a bond, -C(O)-, -C(O)-O-, -$S(O)_2$-, -$S(O)_2$-N(R_8)-, -C(O)-N(R_8)-, -C(S)-N(R_8)-, -C(O)-N(R_8)-C(O)-, and



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24. The compound or salt of claim 23 wherein Y' is selected from the group consisting of -C(O)-, -$S(O)_2$-, and -C(O)-N(R_8)-.

25. The compound or salt of any one of claims 1 through 24 wherein R_2 and R_{2a} are independently selected from the group consisting of: hydrogen, alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, heterocyclylalkylenyl, and alkyl, alkenyl, aryl, arylalkylenyl, heteroaryl, heteroarylalkylenyl, heterocyclyl, or heterocyclylalkylenyl, substituted by one or more substituents selected from the group consisting of: hydroxy, alkyl, haloalkyl, hydroxyalkyl, alkoxy, dialkylamino, -$S(O)_{0-2}$-alkyl, -$S(O)_{0-2}$-aryl,-NH-$S(O)_2$-alkyl, -NH-$S(O)_2$-aryl, haloalkoxy, halogen, cyano, nitro, aryl, heteroaryl, heterocyclyl, aryloxy, arylalkyleneoxy, -C(O)-O-alkyl, -C(O)-N(R_8)$_2$, -N(R_8)-C(O)-alkyl, -O-(CO)-alkyl, and -C(O)-alkyl.

26. The compound or salt of any one of claims 1 through 25 wherein R_{2a} is hydrogen.

27. The compound or salt of any one of claims 1 through 25 wherein R_2 and R_{2a} are independently selected from the group consisting of hydrogen, alkyl, alkenyl, aryl, heteroaryl, wherein the alkyl, alkenyl, aryl, and heteroaryl are each optionally substituted with one or more substitutents selected from the group consisting of C_{1-10} alkyl, aryl, heteroaryl, C_{1-10} alkoxy, -O-C(O)-C_{1-10} alkyl, -C(O)-O-C_{1-10} alkyl, halogen, and cyano.

28. The compound or salt of any one of claims 1 through 27 wherein R_2 is alkyl or substituted alkyl, and R_{2a} is hydrogen.

29. The compound or salt of claim 28 wherein R_2 is methyl or cyclopropyl, and R_{2a} is hydrogen.

30. The compound or salt of any one of claims 1 through 27 wherein R_2 is alkenyl or substituted alkenyl, and R_{2a} is hydrogen.

31. The compound or salt of any one of claims 1 through 26 wherein R_2 is aryl, arylalkylenyl, substituted aryl, or substituted arylalkylenyl, and R_{2a} is hydrogen.

32. The compound or salt of any one of claims 1 through 26 wherein R_2 is heteroaryl, heteroarylalkylenyl, substituted heteroaryl, or substituted heteroarylalkylenyl, and R_{2a} is hydrogen.

33. The compound or salt of any one of claims 1 through 26 wherein R_2 is heterocyclyl, heterocyclylalkylenyl, substituted heterocyclyl, or substituted heterocyclylalkylenyl, and R_{2a} is hydrogen.

34. The compound or salt of any one of claims 1 through 26 wherein R_2 is selected from the group consisting of methyl, (ethoxycarbonyl)methyl, ethyl, cyclopropyl, cyclopropylmethyl, 2-(ethoxycarbonyl)cyclopropylmethyl, propyl, butyl, 2-methylpropyl,

tert-butyl, 3-methylbutyl, 2,2-dimethylpropyl, cyclopentyl, 2-cyclopentylethyl, furyl, fur-3-ylmethyl, furfuryl, furfurylmethyl, cyclohexyl, tetrahydrofuranyl, tetrahydrofuran-3-ylmethyl, 2-(methylthio)ethyl, 3-(methylthio)propyl, phenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 2-methoxyphenyl, 3-methoxyphenyl, 4-methoxyphenyl, 2,6-dimethoxyphenyl, 2-chlorophenyl, 3-chlorophenyl, 4-chlorophenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-cyanophenyl, 4-(dimethylamino)phenyl, 3-hydroxy-4-methoxyphenyl, 4-acetamidophenyl, 4-(methoxycarbonyl)phenyl, 4-(trifluoromethyl)phenyl, biphenyl, benzyl, 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl, 2-fluorobenzyl, 3-fluorobenzyl, 4-fluorobenzyl, 2-chlorobenzyl, 3-chlorobenzyl, 4-chlorobenzyl, 2-cyanobenzyl, 3-cyanobenzyl, 4-cyanobenzyl, 2-methoxybenzyl, 3-methoxybenzyl, 4-methoxybenzyl, 4-dimethylaminobenzyl, 3-hydroxy-4-methoxybenzyl, 4-acetamidobenzyl, 4-(methoxycarbonyl)benzyl, 4-(trifluoromethyl)benzyl, 1-phenylethyl, 2-phenylethyl, 2-phenylpropyl, 3-phenylpropyl, 2-phenylethenyl, phenoxymethyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethy, 1-methylpyrrol-2-yl, 1-methylpyrrol-2-ylmethyl, 1-methylimidazol-2-yl, 1-methylimidazol-2-ylmethyl, 1-methylimidazol-4-yl, 1-methylimidazol-4-ylmethyl, 3-cyclohexen-1-yl, 3-cyclohexen-1-ylmethyl, 3,4-dihydro-2*H*-pyran-2-yl, 3,4-dihydro-2*H*-pyran-2-ylmethyl, 1-methylpiperidin-4-yl, 1-acetylpiperidin-4-yl, 1-benzylpiperidin-4-yl, 2-thienyl, 3-thienyl, thien-2-ylmethyl, thiazol-2-yl, thiazol-2-ylmethyl, 5-isoxazolyl, 5-isoxazolylmethyl, quinolin-2-yl, quinolin-2-ylmethyl, pyrrolidinyl, 3,4-dichlorophenyl, α-methylbenzyl, methoxymethyl, trifluoromethyl, and 2,2,2-trifluoroethyl; and R_{2a} is hydrogen.

35. A pharmaceutical composition comprising a therapeutically effective amount of a compound or salt of any one of claims 1 through 34 in combination with a pharmaceutically acceptable carrier.

36. A method of inducing cytokine biosynthesis in an animal comprising administering an effective amount of a compound or salt of any one of claims 1 through 34 to the animal.

37. A method of treating a viral disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of claims 1 through 34 to the animal.

38. A method of treating a neoplastic disease in an animal in need thereof comprising administering a therapeutically effective amount of a compound or salt of any one of claims 1 through 34 to the animal.